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THE EMOTIONAL COMPONENT OF THE ULCER SUSCEPTIBLE CONSTITUTION*

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THE concept of the human constitution in relation to disease held in this clinic has sought to envisage the individual human being as an organismal entity built of multiple components. The latter have been grouped in the four categories of morphology, physiology, immunity and psychology, and the qualities representing each panel have been studied by whatever dependable methods were available. So far as subjects of gastric and duodenal ulcer are concerned, anthropometric technics [1] have supported the earlier clinical belief that sufferers from that ailment belonged, within variable limits, to the linear division of mankind. Moreover, in the physiological panel of such persons the electrocardiogram has shown a consistent tendency to a long normal P: R interval, a finding which accords with the widely held notion of vagus nerve relationship to ulcer.[2]

The present report presents an inquiry into the character of the ulcer type's psychological panel. It is not an attempt to prove again that such persons are especially sensitive to emotional stimuli. The fact that they are nervous and possess the habit of worrying has long been fully recognized. The purpose here is rather to investigate the emotional quality of the ulcer susceptible male, to correlate it as far as possible with his morphology and physiology and to form some estimate of its quantitative participation in the total reactions of that type of human organism. The ulcer itself may then be regarded as the inevitable product when these specialized human creatures react with certain peculiar onslaughts of environment, as well as with life generally.

Our experience among these interesting people over a period of 20 years or more leads us to believe that in the morphological phase perhaps they do

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not all represent extreme linearity. But even in the stockier forms a definite tendency to gracile bony structure, narrow subcostal and obtuse gonial angles and long narrow teeth preponderates. The linear trend is also seen in their more delicately drawn, longer, narrower faces. There is also found a well defined emphasis upon the feminine component of that curious mixture of masculine and feminine qualities which is common to all human beings of either sex. This phenomenon is known as the mosaic of androgyny. Among ulcer bearers, however, this feminine aspect is not so marked as it is in males who develop gall-bladder disease. As will be seen later, however, the emotional response of the individual to conscious or unconscious awareness of this feminine component (which may be expressed with varying degrees of intensity in any one or more of the four panels of personality; i.e. morphology, physiology, immunity, and psyche) is far greater in ulcer bearers than in subjects with ailing gall-bladders.

In the physiological phase, perhaps the chief insignia of the ulcer patient are found in evidence of autonomic irritability such, for example, as easily sweating palms, tendency to widened palpebral fissure, slight sinus arrhythmia and prompt slowing of heart rate by deep breath holding or pressure over the carotid sinus. It is noteworthy that on admission to the ward most ulcer patients display an average or elevated pulse rate, but after a day or so this falls to a slower than average basic count.

A large majority of our cases have had good to superior intellects. Many possess a keen sense of humor, and their emotional responsiveness is swift and intense. They are often conscientious to the extreme, high principled and are forever striving to attain some goal notwithstanding difficulties which most men would regard as insurmountable. There is never a dull moment in the course of their disease, in their conduct of life and in their conversation. For this reason they are by far the most dramatic personalities on the medical and surgical wards.

Our problem then is to explore the thesis that in a specific type of human being ulcer production is the expression of the total organism's faulty life adjustment, and that this failure rests upon certain inherited and conditioned distortions of psychobiological energies.

The material is drawn from 80 unselected cases of peptic ulcer, both gastric and duodenal. In addition to the routine history which appeared on the hospital chart, each patient was interviewed privately for from two to five hours. These conferences were not devoted to a review of symptoms and diets, but to an effort to study the nature of the man within the patient, his reactions to events, and his attitude and feelings in respect to himself, his family, friends, occupation and life generally. All of these intimate records sound an astonishingly similar theme, but because of their large number and length only a few representative examples are presented here. It may be fairly said, however, that the psychological panel patterns are quite as characteristic for the ulcer potential type as are those of the morphology and function.

As has often been described in the past, it is possible, in many instances, to show that a severe financial loss, business reversal, personal frustration, sexual "sin," or a violent argument has preceded by one to ten days the onset of pain, hemorrhage, or perforation. Such concatenations of events cannot be presented mathematically as proof, but their empiric significance should not be thrown out of court for that reason. Moreover, in the lives of ulcer patients there are many instances in which distressing outward episodes are not followed by any gastrointestinal symptoms at all. Beyond these contingencies, also, there are numerous instances in which obvious external annoyances are of such trivial nature that they can hardly be credited with having precipitated the attack. . Then there are the perplexing situations in which severe peptic symptoms strike unexpectedly when outer life appears to be serene. It must be remembered, however, that in the usual process of history taking we are accustomed to discuss chiefly that aspect of his life which is clearly defined in the patient's conscious awareness and recollection. That, after all, is the only phase of his existence which for him can be; there is no other. Yet from earliest times it has been known that there does exist an entirely separate current of psychic activity which, like a deep subterranean river, flows continuously and with mighty force beneath the superficialities of rational or waking consciousness. This unseen psychobiological energy has ever expressed itself variously and vaguely in dreams, in the occasional paradoxical conduct of intelligent men and in hysterical and neurotic states. In the past the exploration of this inner consciousness of man has been undertaken by many of the greatest medical philosophers beginning with Hippocrates and ending with the contemporaneous systems of Schopenhauer, Nietzsche, Freud, Jung, Adolf Meyer and their followers. For our purpose, however, it is sufficient to accept the existence of this deep emotional current without further discussion and to show that from it, in the case of the constitutionally susceptible person, there may arise traumatic stimuli of the same or greater magnitude and specificity than those from the outer or palpable world. For this reason dream material has been recorded in a few instances. This has not been done, however, for psychoanalytical purposes, but rather as objective evidence that the dream may contain pain-stimulating energy (see J. M., case 24). Throughout the biographical data there is evidence bearing upon the special nature of certain psychic traumata which befall mankind, and also upon the quality of response which so significantly marks the psychological panel of these equally special individuals who are alone able to develop peptic ulcer.

Case Reports

Case 1. E. P. A., aged 37, hemorrhage. January 6, 1937. This man, an Irish Catholic, is a heavy acromegaloid type. His body shows soft, rounded curves, denoting a strong gynic influence.

His father died when he was 10. His mother is living, at 85, in Ireland.

The patient is the youngest of 6 siblings. A married sister lives in rooms

directly above those occupied by the patient and his family. The patient says that his father, a policeman, was a mild mannered man who was never cross nor lifted a finger against the children. Of his mother he says, "My mother did the spanking, she was a huskie. I was a wild youngster—I'll admit I was a divil." He likes his sisters—"one of them still buys all my clothes for me." She has no children.

At the age of 15½ the patient came to the United States (1915) in war time. There was a storm and an attempted firing of the ship by a German passenger. His first job was on the subway, and he tells in great detail (22 years later) all about two men who had been killed doing the same work he did. He said that these experiences did not disturb him. In 1922 he joined a cable gang of the New York Telephone and Telegraph Company and held that job 11 years.

He had been married at 25, on Thanksgiving Day (1925), to a girl 7 years younger. She was red-haired, positive and energetic, like his mother. Their first child, born March 1927, died in a few hours. When asked how the event affected him, he replied, "I felt sorry for her—she got so run down," and "It gave me a spasm of grief, seein' the little mite laying there." The second child, a girl, was born July 1928. "On account of the first experience I was shaky 'til I heard the baby squawk." The third child, also a girl, was born November 1930, when the older one was 1 year and 7 months. The patient had no symptoms at this birth.

Between October 1931 and the winter of 1933 he had two serious accidents, the "flu," and a mastoid operation. The children were respectively two and one and a fourth years old during these events, and he remarked that his wife was very busy taking care of them. Besides this threat to his own security occasioned by the deflection of her attention, he was laid off his cable job without warning soon after he left the hospital following the mastoid operation. At this point, because his savings were exhausted, and with great injury to his pride, he went on Home Relief. His wife got a job, but although her earnings helped, a new fear arose within him that if the Home Relief bureau should discover her action he would be in a bad fix. He lived in this state of fear of discovery from May 1932 to October when he got work on W.P.A. His wife, however, continued her "double timing" so that his fears in respect to the work situation continued. In the midst of this state of affairs his wife became pregnant for the fourth time. He said that when she found out she was pregnant "she raised holy hell and said to me, 'You damned clown, why didn't you know enough not to get me this way!'" He was frightened and humiliated by his wife's violent onslaught and felt the way he used to when his mother spanked him.

His first gastric symptoms started in September 1933, a month after this episode. In addition to his abdominal pains, he had severe cramps and fits of diarrhea (spastic colon?). For the next three years the patient had stomach distress off and on, and on April 26, 1936 he came to Presbyterian Hospital for operation. A normal appendix was found and surgeons reported feeling the crater of a duodenal ulcer. Due to coughing post-operatively his stitches burst and the patient now has an abdominal hernia. The constant bickering with his wife over the unwanted pregnancy went on in the months following his appendectomy. He continued an active sex life, however, notwithstanding his wife's frigidity, but always with an increasing fear of impregnating her. He used contraceptive measures against the Church's orders, and "when I confessed the priest gave me holy hell." These conditions persisted until the present attack which started following his Thanksgiving Day wedding anniversary celebration when he consumed considerable alcohol and food. He vomited blood and the stools were black; there was no pain but a sense of fullness.

Discussion. Thus there appears the picture of the youngest son raising the deuce from early boyhood, perhaps in protest over his mother's greater affection for his older brother. "He was king pin in her eyes," he said. He

adventures to a strange land, and the arrivals of his children are paralleled by his series of accidents and illnesses. Financial insecurity develops, his sister-mother helps, and there is overstriving in the erotic field. He is condemned by his wife for getting her pregnant, and by his priest for not. Financial security and pride further threatened by fear of wife's "double-timing" while he works on W.P.A. Every phase of his life relationships is fraught with fear.

Case 3. T. C., aged 38, pain, hemorrhage. This soft, nearly beardless, rather eunuchoidal-looking man of 38 lost his father when he was 2 years old. An only child, he was entirely supported by his mother who worked her fingers off for him until he was 14 years old. "My mother," he said, "was the truest in the world, very solicitous of me and gave me everything." He admitted being completely absorbed in her "for she was a swell mother to me." He remarked that he had a fine relationship with his employers who, he says, "think well of me."

When he was 20 he married a girl who was one year older than himself. His mother was still living at the time, but he and his wife moved away to their new home. Yet although he moved physically-speaking, a later statement clearly indicates that his unconscious ties, especially in respect to his food, remained very strong. He pridefully continued, "I'm still with the same woman. She runs everything; I just turn my salary over to her, and that's all I have to think of." His family consists of two boys and two girls, ranging in age from 16 years to 3½, and he says that he had no symptoms during any of his wife's pregnancies and labors. The arrival of the first child he took without any special emotional reaction, "but," he added, "they're (the children) more affectionate when smaller; they get their own ideas as they grow up and go to school." His sex relations with his wife have never been very active. "I'm not greedy for it. In fact, I'd not miss it if it never happened." This attitude is somewhat paradoxical when compared with his appalling self-confidence and cocksure talk.

He came to this country one year after his mother's death when his third child was one month old. Before he left Scotland he had noticed some indigestion. In commenting on this he said, apparently forgetting that after his marriage his wife had done the cooking for him, "but certainly those attacks must have been after my mother died because she always prepared my food specially for me, and I could always eat." He was successful in securing a job at once on his arrival in America—"No trouble at all," he said with utmost assurance. "Anyone can get a job if he wants. I'd dishwash if I had to, rather than be dependent on anyone." Thus he jumped unhesitatingly from a Scottish coalminer's job in his homeland to that of a grocery clerk in New York and settled his family easily, admitting that his wife was the boss. "She manages the children, but I hold the discipline over them," said he, with a knowing wink, "when she asks me."

In this country he had no indigestion until January 1933, 4 years ago, shortly after the birth of his fourth child. During the succeeding years he has had occasional spells of dyspepsia although no striking emotional upheavals occurred, but it may be mentioned that he has been earning $35 a week for the support of his family of six. "It entailed some sacrifices to live on it," he said. "We couldn't go to the movies, but I don't bother about the movies anyway." The present attack started three weeks ago with pain and tarry stools. Two or three evenings before the hemorrhage the patient, as chairman of Church building committee, had been carrying on a fight to raise money for a scheme he had evolved for new church work. There was great resistance to his plan. The opposition group criticised him sharply. Though the plan finally went through he was unable to work in its operation because

of the bleeding episode. "I'd have felt much worse if I had failed. But I had no thought of that. But," he continued, with a proud smile, "I've had no pain or bleeding since coming to the hospital." Here, at least, he finds a respite from "the sacrifices" which deeply humiliate him, and from the critical opposition in his church.

Just before the patient returned to the ward after our last conference he suddenly asked, without any connection with the topic under discussion, what I thought about the cause of divorce and all marital troubles. He had given much thought to the matter and was convinced that the unwillingness of both husband and wife to take responsibility, and above all the use of contraceptives were the main reasons. "Children have no mothers anymore," he continued, "because of divorce—and prospective children who are unborn because of contraceptives are denied the benefits of having parents." When I remarked that he had had no father he ever knew, he replied, "No, but I had a mother which made up for everything." From this he proceeded to tell how he never picked fights—"But if anyone laid a finger on me, I'd give him a good smack on the jaw. I'd be the first then." Apparently it had always been his ambition to be first in everything. "If any man beat me the first time my desire was always to beat him the second at whatever it might be."

Discussion. This patient presents obvious eunuchoidal stigmata with strong feminine emphasis. The stimulus of the latter in raising his compensatory masculine bluster is clear. The maintained dependence on the mother and the ever-increasing threat to his male ego of the enlarging family is likewise apparent. The strange conceit of contraception as providing the threat of orphanage to unborn children again emphasizes his own intense dependence upon the mother.

Case 6. J. C., aged 38, pain, two hemorrhages. October 11, 1937. A pale, slender, earnest-looking young man whose father was killed by a truck when he was 19 years old. The mother is living and well at 76. She has a strong constitution and is still active.

His father, whose word was law in the home, had a dominating personality. The older brother (6 years older than the patient) ran away to Canada at 15. This left the patient as "oldest son" and much responsibility was given him. "I didn't know my dad as a man. He whipped us a lot." The patient feared him greatly and considered him to be hard and relentless. "He never praised us to our faces." His temper was terrible. Once when unhitching the wagon the patient forgot to take the trace off one whiffletree and the horse ran away and broke the pole. His father took a fragment of the broken pole and beat him. His mother intervened, as she often did, saying, "You'll break his leg." The father had no pets unless it was an older sister who was mentally handicapped. He was very tender to her. The others all got the same rough treatment.

His mother was a generous, patient soul whose first love was Dan, the oldest son. He came back after his Canadian flight, like the prodigal son. His mother regarded the patient with pity because he worked so hard, hence he welcomed the chance later to enlist in the army. It was evident that his father completely dominated his wife, as he did the children, so that when he died, leaving her the farm, she and they were quite unable to manage it.

He says that there was not much rivalry between the brothers, and that he was especially attached to Dan, the oldest. "He was my hero brother and was killed in the war."

After his discharge from the army in 1919 the patient passed through a period of indecision about religion. He had fought sex desire while in France on the ra-

tionalized basis of fear of disease, but suddenly one night he saw the futility of his life and decided to go into the ministry. "I got religion then and awoke the next morning with a great sense of peace and security." At the denominational college, where smoking was not allowed on the campus, he met two girls, one very good looking and one who would make a good minister's wife. Though physically drawn to the former, he shunned her and cultivated the other's society.

After four years at college he went to the Theological Seminary, having become engaged to the good looking girl after all. At the end of a year in the Seminary he found himself exhausted and depressed because of financial restrictions, and especially because he was unable to compete socially with his classmates. "I was pressed financially," he said, "and resentful that my friends could go to the opera and I could not." This situation led to violent conflict within himself as to whether or not he should appeal for assistance. The struggle between his desire to keep up with the Joneses and the hesitation of his masculine pride to call upon his fiancée for help became acute, but he yielded and wrote to his fiancée who thereafter sent him $10 a month.

Shortly after this letter was sent he had a sharp attack of vomiting and diarrhea which was ascribed to appendicitis, but an operation disclosed a normal organ. He was married a year later and during the ensuing three years he had gnawing pains off and on, especially during his wife's first pregnancy. At this time also he was in controversy with two factions in his church and resigned. His symptoms did not increase at the time of the child's birth, but he was disappointed that the baby was a girl. After the resignation he was taken in by a friendly preacher so that he and his family were supported.

In May 1936 he was in violent disagreement with the general assembly of his church in Syracuse to which his wife and 3-year old daughter accompanied him. When he returned at the end of the month, he was greatly embarrassed at facing, on his first Sunday appearance, a highly critical and divided congregation. "I felt I had been repudiated by the Mother Church." The patient also said that he had been upset all spring because his wife had had a miscarriage in January 1936, and that she was two months pregnant at the time of the Syracuse convention. His first hemorrhage occurred on June 3.

In connection with the above precipitating episode it should be reported at this point that the patient stated that his sex adjustment had never been satisfactory, and that because of ejaculatio praecox he had always practiced withdrawal as a contraceptive measure. He was conscious of guilt in respect to any contraceptive plan because it "ran counter to nature's purpose." There was much residual guilt over early masturbation. Superimposed upon this chronic fear and guilt there was now added the double blow—the Mother Church had failed to accept him and his wife was already deflecting a large share of her maternal energy from him to her three-year-old child and new embryo.

The following November the patient was very busy getting ready for a church entertainment and picnic. On November 25 he and his wife worked late at the preparations. On the following morning his wife awoke feeling very ill and unable to continue helping him. Although he knew she was pregnant he suddenly felt "lost, alone, and out on a limb." He then had a tarry stool.

Discussion. (1) On the farm the patient worked hard and got mother's sympathy and approbation as well as food, clothing and housing, i.e., working hard in a protectorate.

(2) In theological seminary worked terribly hard, but he had scholarship, and his fiancée sent him money. So again he had her sympathy and

approbation as well as food, clothing and housing (protectorate). The first vomiting and diarrhea came when the support was insufficient for both physical and ego needs. Fiancée's funds supplied the latter. Then he was better.

(3) When he took his first parish he was self-supporting and his wife was not working. This was his first experience at working hard outside of a protectorate. Although thrown out by his church he was taken in by a friendly preacher, and even though his wife was pregnant and the child became an added burden, he was adequately protected.

(4) Again at his second parish the patient was on his own. Having had his fingers burned once, he had the sword of Damocles hanging over him, lest he express philosophies which would result in his being dismissed. Thus he may not have been true to himself, and so a new set of wheels within wheels appeared for his conscience to digest. His hemorrhage followed the convention as he took up his preaching again, and faced a possible recurrence of his original dismissal.

(5) The second hemorrhage. The patient knew of his wife's pregnancy. All during the preparation to feed the crowd he consciously grew more and more resentful that she was pregnant and that he would have to carry the major onus of the exercises. Then when she was sick and "let him down" on Thanksgiving morning, a black stool appeared. Fear and resentment—she had forsaken him.

Case 9. J. F. D., aged 28, pain. The patient's father at 55 years of age is a hypochondriac, always taking medicine and displaying constant gestures of his hands. The mother at 50 has complained of stomach trouble for two years. She was seized two years ago with the idea that she was going to die. She told the patient's wife but not the patient. However, the wife told him two days after his admission to the hospital. "Mother has not had an easy time with Father," he said. "He runs around, out at night. It's because Father deceived her all these years that she suspects everyone." The patient left home twice because of her constant nagging. "My mother runs everything and completely dominates her family. She was always right, regardless of the facts."

The patient is the oldest of three boys. The youngest is six years younger than he, yet the patient does not remember his birth. At the age of 10 he first remembers his brother, whom he was forced to take care of like a nurse. He recalls only the fact that the baby brother was continually soiling himself, and the patient had to take him in and change him. The patient used to chastise the baby a great deal for this.

As the two brothers matured, the younger one got a good high school education and went to work in a life insurance company, advanced rapidly, married and took his wife home to live with his mother. The patient speaks sneeringly of the brother's course and says, "He is perfectly satisfied to live with Mother and lacks spirit to pull away and set up his own home, and anyway his wife has him right under her thumb."

The patient, on the other hand, joined the Coast Guard at the age of 18 years and after three years entered the merchant service, seeking adventure. (Masculine protest.) He had ambitions to become a navigator, but he was continually being disciplined, and finally discharged, always because of being involved with women.

"Women have always been my downfall anyway," he said. He married in 1933, a girl whom he had known for a year. She had an excellent education, graduating with honors from high school, and had advanced to a good position in the same life insurance company as the patient's brother. The patient says of her, "She has a good head on her shoulders. She tried to put it over me at the start; not that she tried to boss me, but she resents my telling her what to do."

The first baby arrived nine months after their marriage, February 1934. The patient was then doing night work in a "speakeasy." The pay was good but the work was risky, involving the danger of arrest or hold-ups. The patient had been working at this job a year before he married and had led a very careless and wild life, drinking heavily, and although engaged to the girl, indulging in promiscuous venery. He was always greatly troubled with ejaculatio praecox. He had been faithful to his wife during the first years of marriage and says that his sex adjustment with her had been good. Although he and his wife are Catholics, he declared with slight braggadocio that he proposed to "disregard the rule against contraceptives."

The patient was informed by his wife of her pregnancy while dancing one night at a party. She said that it was only six weeks before her confinement. On hearing that he said, "I felt as though the world had dropped from under me. What would we do with all the bills we had? I certainly would have tough going; bread without butter, and coffee without cream. When I realized she meant it, I wanted to rush out of the place. It was just like someone telling you, 'We are going to take off your leg now,' and what would I do without a leg? The news was too soon before the event, I wasn't eased into it—I wasn't prepared. It was a terrible blow. I got to arguing with her because I thought she had been holding out on me. I was angry and surprised—all in one."

During the four or five weeks before the baby came, the patient had pronounced stomach symptoms, and he began drinking milk instead of coffee. The stomach pains continued all through the year, with occasional periods of relief.

With the second pregnancy, as with the first, she delayed telling her husband until about two weeks before she went to the hospital for delivery. From the moment she told him he had gastric pains and lived on milk, crackers and cereal. "My mother told me," he said, "that my wife has an easy time, but that I have the pains."

About four months following the arrival of the last baby, the patient had a small hemorrhage which came on after an emotional upset at home. He said of this episode, "Lots of times I want my wife's company, and want her to fondle me, and often I want intercourse, but the babies would cry or need something, she would go to them and I would have to wait. In fact, I resented the babies—did not want them. When she would go to them I would feel the same as though a competitor took her away from me. I would want to kill him. As a matter of fact, I even threw books around the room. It burned me up inside. Then when I got out in the street I would realize what a darn fool I was, and that the baby needed her more than I did."

After leaving the hospital he drove a truck for a year and then entered the police department. He was a rookey for three months, then on patrol. In September 1937 he felt the strain of this work—later in 1937 he had return of pain. Had worked regularly in daytime until he went on force. Then irregular police life, night work, etc., nervous, irregular eating and sleeping. In 1938 he was put on a police boat and things went better with regular sleep and less dangerous type of police work. Following this respite, however, his appetite waned and pains increased especially at night. He resumed diet with benefit for three or four months. This he ascribed to further loss of sleep and trouble with his sergeant for breaking rules. He was upset at the thought of his captain's criticism.

In November 1939, he was driving his own car on a slippery pavement and

collided with a peddler. The latter was knocked down and the policeman on duty took his name. "So there I was, a policeman myself, arrested for dangerous driving." That night stomach pains began and lasted for six to eight weeks. He had bad dreams that the Jew peddler died and that "they blamed me." This attack cleared up in three or four months and he remained well until something else happened. The next severe attack started in mid-January 1941 following a fight with his sergeant about not reporting on the hour. That attack continued until March 3 when it was immediately relieved on entering the hospital. His obstruction was operated on and he felt happy at the thought of an operation.

He has been well since the operation until he lost his temper with his wife two weeks ago and was conscious afterward of stomach pains and loss of appetite. He recognized that the coming and going of pains are clearly related to emotional tension and its relief.

Discussion. One might summarize the mechanism of this man's emotional reactions in the following way. The patient began by being jealous of the younger brother whom he had mothered. This was intensified by the younger brother's prolonged control of the actual mother's concentrated attention. The patient exhibited an intense masculine protest in compensation for his inwardly sensed feminine component. Again, as in the former case, we see the desire to take milk and soft foods when the mother's attention goes to his "rival" children. So he remains a little boy, always frightened that someone will criticize or punish him and that the wife-mother will take her attention away to rival brothers.

The case further illustrates the obvious impossibility of obtaining any successful result by psychotherapy after irreversible tissue change has set in causing obstruction.

Case 14. J. G., aged 55. This Englishman came to America at the age of 21 and lived here alone until 20 years later. He is the second son in a sibling group of 11, seven of whom were brothers. The father's attitude to the patient was gentle and the latter did not fear him. The mother appears to have been a very lovable person, and the patient, with lowered eyelids, admits that he was her favorite and that he worshipped her. He was never a good mixer, was retiring, no scrapper, and had few friends. He always possessed a nervous stomach which responded adversely to personal criticism. Consequently, he has always tried to do right so as to avoid complaints. There is a marked emphasis on the feminine qualities in his make-up. As a little boy his habit was to hurry home from school and become, as he says, a nursemaid for his mother, helping her take care of the many younger children. This experience he said led him into his present occupation of butler. He has never had difficulties with his employers and has always held his places for long periods of time. His mother's death when he was 40 upset him emotionally to such an extent that he imposed upon himself a year's mourning during which he eliminated all pleasures from his life. Whenever he heard music which his mother had liked he wept, and recalled that as a small boy music made him run and bury his head on his mother's knee.

His marriage, which occurred one year following his mother's death, has been childless although his wife did have one miscarriage. His wife and mother-in-law live together in an apartment while he stays with his employer. Thus his married life has consisted of hectic trips and early starts to make possible visits to his wife. Consequently he has never dominated his own home.

The patient had the unusual experience of two severe hemorrhages separated by a time interval of 25 years. In the fall of 1915 the patient, then in apparently good health, had just left a job when he received word that one of his brothers in the British Army had been killed at Nieuport in Belgium. The mother was also greatly depressed because she had not yet fully recovered from the death of her own husband, the patient's father, 18 months before. A few months later he found a new position as valet and steward on a house-boat. His employer was himself on a strict ulcer diet. On his first day he had an altercation with the captain about his duties. The point of issue was whether he should do crew's work or valet's. He refused the former, saying that he was employed as the valet and not as a sailor. The episode suddenly awakened him to the realization that he was doing, as he said, a woman's work and that he was either afraid or incompetent to do work which men did. Three days later his stomach pains began. Furthermore, all during this period he was disturbed by the fact that all six of his brothers were fighting in the British Army. He had many struggles with himself as to whether or not he, too, should join up. He turned his back on the issue, nevertheless writing one of his brothers advising him never, under any circumstances, to consider going into domestic service. On his return north in May 1916 he received a letter from his mother in England, stating that his youngest brother, who was under age, had run away from home to join the British Army. His mother took the boy out, but after a few weeks the lad again ran away and this time the mother did not interfere. The patient admitted he thought him very plucky; he censured himself for clinging to his security and felt the humiliation of the feminine tendency within himself. He also reported two dreams at that time which were quite clearly related to his early days at home when he assisted his mother in taking care of the children. Two weeks after the letter arrived he had his first severe hemorrhage.

During the intervening 24 years there were occasional little acid eructations but he worked adequately, was married, had small difficulties with finances in connection with the loss of a house which he had bought, etc. The present hemorrhage, which occurred on June 22, 1941, developed in the following setting:

His employer's family, on June 19, was about to move to Maine for the summer. The chauffeur, who was a fine mechanic as well, was not to go. The butler was told that he must drive the station wagon with the luggage and the other servants, who were all women, to the summer place. He resented doing the chauffeur's work just as he had that of the sailor and three days later entered the hospital with severe duodenal blood loss. The episode presents an analogy to the yachting experience of 24 years before. Both seem to have been precipitating factors. An emotional situation related to the present war was also involved. The patient says that on the conscious side he has been very little concerned about this war, but in a recent letter from his widowed sister-in-law, whose husband had been killed at Nieuport, he learned that her sons, now in their twenties, were fighting with the Australians in the Mediterranean. When the battle of Crete took place about June 1, he began to wonder and worry whether his nephews were with the Australian regiments which were known to be in Crete. This campaign occupied the early weeks of June and symbolically recapitulated the episode of the death of his brother in Nieuport 25 years ago. His anxiety and self-criticism for not having joined up like a man mounted steadily until the precipitating episode and hemorrhage of June 19.

Summary. The remarkable circumstance that two hemorrhages were separated by a period of 25 years. This individual presented a psychobiological conflict related to the androgynous mosaic. He was conditioned

by his mother and his occupation in such a way as to augment his strongly emphasized gynic factor. As the result of a small superficial episode (brass polishing on a yacht) a bitter realization of the difference between men's work and women's work brought to consciousness the basic male fear that he will fail when the crucial test arrives. The World War provided that challenge, and he failed. Twenty-five years later at a time when he resents the nature of his work and this resentment is consciously expressed by an attack upon the limitation of his personal freedom and the necessity of doing chauffeur's work (again a man's job), the war situation involving his male kin obtrudes itself with exactly the same challenge.

Case 16. L. G., aged 38, severe, repeated pain for years. The patient was originally the second of nine siblings, now the oldest of six. Father's attitude to the patient was kindly. The mother, on the other hand, was a severe disciplinarian and taught the boys to fight anyone who attempted to thwart them. She continually told the patient in childhood that she would "knock hell out of him" if he showed fear. Notwithstanding this ferocity on her part, the patient was her favorite and has still, at the age of 38, been unable to leave her household and set up his own establishment, either as a bachelor or married man. Furthermore, she never displayed the slightest physical demonstration of affection. The patient's next younger brother became a prizefighter, and when the patient was 17 and 18 he used to watch his brother fight. As he watched he became terrifically excited, broke out into heavy sweats, his heartbeat changing from rapid to very slow thumping and he would have turning sensations in his stomach. "It was just as though I was fighting my brother's opponent myself and wanting to knock him out." This was in 1920. In 1925–26 when he was 22 years old, after six years of this vicarious pugilistic interest, he had his first stomach pain. At this time, too, he nearly married a girl with whom he had been carrying on a sexual relationship, but he suddenly retreated and started an affair with another girl. The second girl he described as revolting to him because of her excessive hair distribution. During this affair, which lasted eight months, his stomach was continually uncomfortable. Both these girls were energetic and aggressive, "as bad or worse than my mother."

During the first interview in which this history was obtained the patient was resistant, viewed the questioner with suspicion and nervously twitched about in bed, complaining of his pain. At one point he said, "I wonder if the Lord is punishing me for my sins." He remarked that he couldn't see what discussion of his intimate life history had to do with his ulcers. He was bitterly aggressive toward Dr. Blank who had explored him some years before and who had told him that he would never be well. Furthermore, the patient resented the fact that Dr. Blank had been angry with him and disciplined him for not keeping the diet which the doctor had prescribed. "Even today," he continued with great excitement, "Dr. Blank hasn't taken two minutes of his precious time to come down and see me and say, 'Howdy, kid.' He knew I was here four days ago and hasn't been in yet." His attitude was very suggestive of a piqued girl. In this connection it was interesting to note that notwithstanding the tremendous dynamism in the psychic phase of the personality, with the powerful aggression, virile muscular gestures and the history of fighting, the patient's bodily contours were rounded and displayed a strongly gynic emphasis.

It is a matter of some interest to compare the two histories, one routine hospital and the other the special history, of the patient's reactions to life:

Hospital history	*Special history*
April, 1930	
Following a year or so of indefinite pains in the abdomen, sometimes in the upper part, sometimes in the right flank, patient entered hospital for an exploratory, the gall-bladder being under suspicion. The preceding disturbances had been satisfactorily related to dietary indiscretion. The patient was an enormous eater and frequently over-indulged in alcohol. At operation a normal gall-bladder was found, but there was a thickened area in the posterior surface of the pylorus which was taken to be an ulcer. No further surgery was done and the wound was closed.	The evidence for early stomach sensations has been presented in the foregoing personal history and the very definite stomach pains and indigestion which began in 1925 when the patient was 22–23 years old occurred over the period in which his emotional conflicts were at high tension in respect to romantic affairs and the problem of marriage.

It appears from the record that between the years 1930 and the present admission in 1941, the patient was in and out of the Out-Patient Department and the wards, there being in all five admissions to the latter. During these years such notes as these were found:

Hospital history	*Special history*
12–8–30. Medical treatment is unsuccessful in this case to date because he has not been living up to dietary advice. It is suggested that he be admitted to Medicine for straight Sippy diet. 12–11–30. Readmission for another try at Sippy diet. As he improved and had remained 5 days without pain the following note appeared: "It doesn't seem unfair to assume that his pains outside the hospital are probably due to indulging his own tastes." 1–1934. A series of notes, all emphasizing the patient's "lack of coöperation" in the matter of following his dietary instructions. 4–1–37. "Same old story. Seems to get along well as long as he sticks to diet, but 2 or 3 times a year has recurrence of pain." At this same time a roentgen-ray showed the presence of a prepyloric ulcer.	During this period from 1930 there is one letter from the patient to the Social Service Department making excuses for not coming to the Clinic because of business engagements and economic pressure. There is, besides, a reference on 8–24–35 to an operation which had just been performed on his father for supposed carcinoma of the prostate gland. The doctors had told the patient that the old man could not live more than 6 weeks and sent him home with that message. "The sudden shock of this," writes the patient, "left me in poor shape with plenty of pains, even though before this experience I had been well."

Paralleling the hospital notes of dietary indiscretion, the special history discloses the fact that frequently during the same period the patient was involved in violent altercations with members of his family. As the oldest son he considered himself the representative elect of his mother. Whenever any one of his siblings in his judgment misbehaved he gave them first a tongue lashing and often an actual beating. Thus, for example, within the year he had a tremendous argument with and delivered a tongue lashing to his sister-in-law for not controlling her husband (the patient's brother) for spending too much money on her. During the same year he actually knocked his brother out with his fists for gambling and losing so that the patient was forced to help him out financially. The patient evidently was violently criticising his sister-in-law for not doing what the patient's mother had done to him and his father. He also admitted that his fear of losing money was always present in his mind. All of these outbursts were followed regularly by increase in stomach pains. About 10 days before his last admission on April 13, 1941, the brother's store was destroyed by fire and the patient lost considerable money as a result. Four days after the conflagration the severe stomach pains which brought him to the hospital developed.

During his stay in the hospital several minor episodes of pain occurred, one or two of these at night. For example, he had pain immediately after lunch on April 18, 1941,

which he blamed on a boiled potato. Further questioning, however, brought out the fact that during luncheon he was reading the account of the episode of the Esposito brothers who, as the patient said, "attacked and killed their victims like mad dogs." He then continued, "I felt my stomach curl up inside as I read." On April 24, 1941, the patient woke at night with pain. He admitted, however, that he had awakened suddenly with stomach pain from a dream in which he was engaged in a terrific fight wherein he was attacking violently. It was interesting in this connection that for the three previous days the patient had been on a full ambulatory diet without any discomfort. He further recounts a pain which occurred in the middle of the night one month ago, immediately following being awakened by his mother who was feeling ill. He said that his first reaction toward his mother had been resentment at having his rest disturbed; and this morning, April 24, 1941, the nurse awakened him from a mid-morning doze. He resentfully asked her what it was all about and within a few minutes pain developed.

Discussion. This patient displays admirably the ruthless bluster and violent aggression in conduct toward the outer world, but within, supported by his strongly feminine emphasis in both soma and psyche, he is like a girl child, unable to leave a dominating mother and striving to emulate her and retain the favorable protectorate in which she holds him.

Case 17. A. H., aged 32, indigestion, hemorrhage. March 23, 1940. This patient is a sturdy American of German descent. He entered the hospital for blood loss, with symptoms of dizziness and tarry stools. He had had gas pains for several months. His routine hospital history was typical of those given by peptic ulcer patients. Both his parents are living; they are Catholics, and the patient was strictly brought up in the Church. He was married 11 years ago at the age of 21 and has a daughter 10 years old. Four and a half years ago, in 1936, he was divorced. His wife soon remarried and his daughter was adopted by the second husband. He has been a rather heavy drinker.

Shortly after his divorce he began keeping company with a girl who was a few months older than he. The relationship developed into an actively sexual one during the latter half of 1937, 1938 and 1939, when it became, as he said, "more like a marriage." Indeed, he said he would have married except for the economic situation. This was the only reason he gave at first for not marrying, but later on he admitted that he feared the church's attitude. "They would excommunicate me if I remarried, and that would break my mother's heart," he added. In this connection it is of interest that once when quite drunk he started to enter his priest's house to ask the latter why he couldn't marry again. The priest sent him away and told him to come back when he was sober, but the patient never returned for the discussion.

This conflict obviously had been "burning him up" since the complete sexual relationship had been established in late 1937. His first indigestion occurred in December 1938 following difficulties with his employer whom he felt was treating him unfairly. The mild indigestion continued off and on until August 1939 when he had a violent altercation with his boss which led to the loss of his job in October. He was unable to get another job and returned to live with his parents. His fiancee was also living with hers for a similar economic reason. From then until his hemorrhage in March 1940 the patient had recurring attacks of pain.

There had been a disappearance of all symptoms for a period of two weeks in the early part of March, and the patient felt well and enthusiastic. He told his fiancee of this and suggested that they marry immediately. To his surprise and annoyance she refused, saying that she wouldn't marry until her parents "are gone." "My brother walked out on them and I shouldn't do the same." This conversation occurred

late on Saturday night and three and a half to four days later the patient had a hemorrhage. His companion had repudiated him in favor of her parents.

It was suggested to the patient that he seemed to be waiting for his parents to die in order to marry. "I'm waiting for no such thing," he snapped resentfully, on the defense. "I'm having fun trying to keep my father younger."

A dilemma confronts the patient. If he marries he faces excommunication and so breaks his mother's heart, or he continues to live in sin and so is oppressed by guilt and fear of punishment. His economic security is dubious and his girl in the end forsakes him.

Case 23. G. McP., aged 41, perforation. July 29, 1940. This man, showing strong gynic emphasis in both morphological and psychological panels, had been a fine soldier in the great war. He went over the top many times with fear in his heart, but showing perfect action courage. He was moderately gassed and wounded in the knee. After the war, at the age of 20, he came to Canada with his parents and sisters. Six years later his father left and returned to Ireland with his oldest sister. Then, after living for eight years with his mother and two sisters, he tried living by himself, but at the end of two years he returned to his sisters who were then both married.

During the following years, 1926–36, the patient said, "I was always looking for excitement, women and liquor." He tried giving lessons in motorcar driving and also worked himself as a taxi driver, but, said he, "I couldn't stand it. The strain of avoiding accidents gave me pain in my stomach every two or three days." Then he moved to Chicago and New York during 1935 and 1936, still driving taxi and teaching, and still having pain. Finally in 1936 he began living with the woman he was subsequently to marry. She was a divorced and childless woman who was four years his senior. He had not been altogether faithful to her during the period of their relationship and subsequently was very active and promiscuous sexually, but he always feared she would discover his "bad behavior." During the 18-month period just mentioned, the patient plied his newly acquired trade of hairdresser and found it meticulous and responsible work. He continually feared he would not do a satisfactory job or might burn his client. It made him feel tense and nervous. In 1937, while still living with his mistress, he started a clandestine love affair with another woman. He lived in constant fear of discovery. One afternoon in February of that year he met his second paramour at a New York hotel and began drinking at once. "I was very nervous and apprehensive." Between five and seven o'clock he had two sexual encounters and at two a.m. his ulcer perforated.

An emergency operation saved his life and during his recovery his first companion decided to take him back and "take care of me." Three months after the operation they were married. The marriage was a purely maternal affair and conjugal relations were never reëstablished. The patient's stomach symptoms were almost negligible for about a year and his general health good. At this point he resumed clandestine love affairs and almost at once his pains began again. He recognized their relationship to his fear of discovery.

Discussion. The patient said that he had always tried to please everyone lest he lose friends and that the same thing applied to his sisters and mother. He knew he had been excessive in sexual matters and had sought adventure and violent activity far too much. These trends seem to point to compensatory efforts in view of his marked effeminate appearance and manner and the choice of his final occupation.

Case 24. J. M., aged 25, pain, multiple bleedings. This gentle, girl-like youth was the youngest of four siblings. He was 17 when his mother, to whom he was inordinately attached, died suddenly of heart disease. In speaking of her he said,

"Anything you wanted, you'd get." It was rumored that an older brother, Francis, was her favorite, but the patient quickly added that she herself had denied that. After his mother's death his father tried to take her place with the children. "He can't do enough for us, prepares our breakfast, and has spent $2000 on my stomach in the past three years and I've never heard him mention it." Both the older brothers are huskier than the patient, but both have "weak stomachs." One of them probably has an ulcer.

In speaking further of himself he said, "My brothers treat me like a 3-year old. Whatever I did was always wrong. If I bought a suit or hat or ties, no one liked them." He was never abused physically and was always the baby. The brothers are pretty strong. One, Francis (ulcer), is of the patient's height, weighs 185 (pt. 145 highest). Thomas is 6 feet and weighs 200, he is a physical instructor and a fine athlete. The patient played baseball, but in the past two years has felt himself going backwards, slipping, perhaps "growing old." He recalls that he always had a poor appetite at table and picked at his food. His brothers would say, "How do you ever expect to get big and strong like us?"

He is a sensitive, mild lad, with a rather dreamy look and not much physical energy. There are swift little facial twitches and a habit of swallowing often. He always has noticed his hands, which he thinks are small in comparison with those of other boys of his age, yet he could do as well with them. He never went in for scrapping but could hold his own if molested. He knows he has small bones but has no sense of genital inferiority.

"Since my brother had an ulcer and he is older than I, and the oldest boy, and Tom also has a weakish stomach, I feel that I should have a worse stomach than any. I'm more nervous and frighten easier."

Episodes of pain or bleeding

1933—Loss of mother. First, after mother died. "At Mother's death I was very grieved and had an all gone feeling" for three months. "It never went away completely. A year later I consulted a doctor for it. I kept telling myself that I was old enough to take care of myself, but yet inside I knew I couldn't. You see, I was so much younger (eight yrs.) that I was very close to her, and felt that my father was very distant. I never knew him until lately."

1935—Aggression and insecurity. Second, pain, then operation. His first job after leaving school at 17 had been at a soda fountain. A colored customer threw an ice cream cone at him which he threw back, hitting her. He left in a great temper and had stomach pains all through the day and all night. Then he got a job as a porter. It was hard work and boring, irritating trying to get his loads through doors, etc. Increasing pains led to operation, 1935. Even though he hadn't liked the job he tried to get it again after the operation because he had a driving eagerness to work.

1937—Sex guilt and fear of failure. Third, bleeding. At the time the patient was having occasional sexual intercourse with a friend. This became an established relationship, but he admitted it was always associated with guilt, fear, and solicitude for the girl. At the same time he had been put on a job in a linen house where his foster sister, who was also his first cousin, worked. She nearly drove him mad. His job was desk work with problems to solve, real mental work. The patient always felt afraid that he couldn't do it as well as it should be done.

1938—Loss of miniature mother. Fourth, hospital admission, pain and bleeding. Under the dictate of his conscience he parted from his girl on January 1, 1938, six weeks before admission. He states definitely that his stomach was worse after the break. He used to be able to talk his symptoms and troubles over with her. So he

lost his second mother. For two weeks before admission he lived on crackers and milk and eggs. He imagined that his stomach was "full of ulcers."

Pain "this morning." One morning shortly after his admission to the hospital he reported having had a bad dream during the night. "I saw my girl on the roof with her mother. I fell, either off the roof or downstairs. I was frightened when I saw her mother and I backed up and stumbled in the get-a-way." The occupant of the next bed reported that while dreaming the patient had his hands pressing on his stomach and was moaning, but he didn't wake. The patient says, "Perhaps bringing the girl into our talk yesterday may have stimulated the dream." He thinks the girl's mother must know of their relationship, and he always feels awkward and guilty in her presence.

He often dreams of falling off great heights, and always feels squeamish and gasps with fright when looking down from high places. He thinks there was some talk of his having been dropped as an infant.

On returning home after his discharge from the hospital he had an irritating session with his family. His policeman brother drove him home, and on arrival he found his sister with friends. He was annoyed and sulked on the roof until they left. They were from the store where he and his foster sister work and he didn't want the relationship known. When they left he came down to find that no supper had been prepared for him. He was furious and in addition it made him late for a date with his girl. Pains followed in a couple of hours.

On some days he says he can't think and is confused. On those days his job goes badly, yet he feels and knows he can do far better. Being a Catholic, he went to Novenas to try to help himself, but he didn't attend regularly and then chided himself for his delinquency. This effort was of 1940 and during that year his stomach was never better—no pain. In June 1940, however, after he had ceased attending the Novenas, he had sudden bleeding, no pain, no warning. "It was just supernatural," he said. "I knew a few days before that I would bleed." He had become apprehensive about his bleeding attacks so that every time he went to stool he feared he would find blood and was greatly relieved when he saw "all clear." This fear accompanied every stool since leaving the French Hospital in May 1938, especially from June 1940 until now. In previous bleedings he had always a month or more of severe pain as a warning. Now he is terrified every morning that he will find blood.

It would appear that the patient's problem is concerned with fear arising from two sources: one, loss of maternal interest, and second, "sex is sin." Ranged before him are guilt of extra-marital sex relations, a commitment by his conscience to marry the girl whom he doesn't love and doesn't want to marry, and finally fear of losing the mother principle. He is therefore confronted daily, hourly, awake and in dreams, by the symbolic figure of a policeman who actually had frightened him when he was 7 or 8 years old. Consequently, fear of detection and punishment for anything he might do pursues him. Police, priests, and his primitive concept of a jealous and punitive God are merged in an ominous pall above him. In this predicament, hospital nurse and physician stand as the only mother surrogate.

During his last hospitalization he admitted that he had resumed his sex relations with the girl and that he was immediately conscious of a strong sense of sin, guilt, fear, and stomach pain. He said, "I know that marriage will save my soul, but I'm afraid to marry the girl when I don't love her." The situation presents the eternal conflict between man's desire for security and a natural sex life, and the fear of his organismal inability to achieve the first, or exercise the second without condign retribution.

Case 27. A. P., aged 41, two perforations. The patient is a French Basque who lived with his parents until the death of his mother when he was 27 years old. He is a small, quick-moving, hot-tempered man. His first stomach pains appeared when he

was 25 and working as a baker. He had come to the United States with his parents two years before. At the time the pains started he had been gambling a great deal for over a year, much to the distress of his mother. Often he would lose his whole salary and be filled with guilt and fear because it hurt his mother so. "I suffered and felt it in my inside." By constant criticism his mother interfered with his feeling of his right to gamble. He knew it hurt her yet he kept on "falling from grace."

As a child he was always in conflict within himself over his fights. He couldn't stand criticism, interference, being "bawled out," or physically attacked. He defended himself if attacked, but became so violently angry that he was afraid to hit hard lest he kill. He thinks that his mother's continual interference with his gambling instinct and his resentment at her attitude caused his early pains.

The patient married a few months after his mother's death and changed from his former work to the fur industry. The first child was born two years later. He was happy during his wife's pregnancy, and had no nausea or conscious worries. He felt a healthy growing sense of responsibility and gambled less. Though he had been active sexually before marriage he remained faithful to his wife and felt no guilt or fear concerning his youthful experiences.

His fur business, however, did not turn out well so he changed again to the position of elevator boy in an apartment house. With his wife and his four-year old child now to support, he was afraid he might lose his job if he made any mistakes, "and running an elevator is a nervous job." About the middle of June 1933, the superintendent of the building asked him to make secret reports on the tenants. The patient refused and was upheld by the agent, but the superintendent kept nagging him to discipline the skylarking children who lived in the house. Finally one evening the superintendent called him a softie and bawled him out severely. The patient became enraged and just managed to control his strong impulse to smash him. That night he slept badly, ate no breakfast, and went to work at 8 a.m. on his elevator. At 9 a.m. he perforated.

After his recovery he became a waiter, which he says is a very aggravating business. "If the headwaiter doesn't like you he picks on you." It happened that for the ensuing five years he was in a position under constant irritation by the headwaiter, and his stomach was uncomfortable during that entire period. Toward the middle of February for the first time since his marriage the patient became involved in a sexual relationship with another woman. It so happened that by accident, while walking on Broadway with this new companion, he met his wife. He quickly elaborated a story to explain his situation, but that night was severely criticized by his wife, who, he said, was evidently terribly hurt by the experience. He broke off his outside relationship abruptly and for the ensuing two months made every effort to reëstablish his wife's confidence in him. About three weeks later he found that she was spying on him and this threw him into a violent anger. During the subsequent weeks he was never convinced that she had accepted his renewed fidelity, and felt that he was always under suspicion. Not only was he uncomfortable because he was hurting her, but he was exceedingly angry with her for not accepting his real effort to atone. On the evening of May 5 he served a large wedding party dinner at the hotel where he worked. There was some crooked dealing by the dining room captain in respect to the patient's tip. The latter flew into a rage, accused the captain, and threw him downstairs. The next morning his second perforation occurred.

The patient sums up his life story by saying that his stomach was worse after his mother's death and that following his unfaithfulness to his wife he had the same guilty feeling of having hurt her that he had originally had about the hurt to his mother due to gambling. If he were only at peace he would not have stomach sickness. "It is only when I get irritated. Losing my temper is much more dangerous to my stomach than improper food or liquor."

This individual illustrates again the pattern of chronic guilt and fear and the precipitating episodes of violent outbursts of anger.

General Analysis of Entire Group

Because space does not permit printing all 80 records a summary of their content is offered. It should be noted, however, that the fear emotion arising from various stimulating mechanisms is the essential point. Furthermore let it be admitted that all human beings are subject to loss of maternal principle, to sex experience, and to causes for jealousy and aggression. The fear response to these stimuli within each individual, however, is an entirely personal matter, determined by his protoplasmic constitution and the nature of his childhood training and education. Moreover the degree of guilt and fear which is aroused in a young man by sexual experience, for example, is almost directly determined by the early teachings concerning it to which he has been exposed. In our series the quality of reaction to this particular problem seems to have been equally divided between fear and its absence.

Table I

Distribution of Chief Fear Sources as Elicited in the Group of 80 Cases *

	No.	Per cent	No.	Per cent
1. Inner sense of insecurity based on actual or supposed physical inferiority including gynic emphasis	63	84.0%	12	16.0%
2. Persistent hold on mother principle and fear of loss of mother surrogate's approval	76	97.4%	2	2.6%
3. Jealousy and aggression	50	64.9%	27	35.1%
4. Guilt and fear related to sex problems	31	49.2%	32	50.8%
5. Compensatory striving	41	56.2%	32	43.8%

* Out of the 80 cases a few failed to supply adequate information in one or another of the five categories. Hence the total number of cases varies in each.

Discussion

Themes which emerge from the foregoing biographies are apparently related chiefly to the instinct of self-preservation. In the lower animal forms, at least so far as we know, this applies to bodily existence alone. In man, however, there stands in addition the supremely important consciousness of personal identity. For him this ego transcends all else, is defended to the last with his strongest effort, and its injury or destruction may be followed by tissue deterioration or death. Thus, while organismal reaction in the interest of survival is common to all living forms, and expressed as expediency dictates either in advance or retreat (fight or flight), man's conduct in these respects presents complex and often paradoxical patterns. Moreover the unpredictability of human behavior may be influenced by a person's estimate of his own capacities. Such judgment, however, may often be unfavorable because of the condition-tinted lenses which each man dons in early childhood and wears throughout life.

In the depths of inner consciousness, all human beings, especially males, depend for their sense of security primarily upon sound and powerful bodies—consequently there are in the main two somatic factors which may operate to undermine self-confidence. The reaction to these structural implications seems to be most intense in peptic ulcer subjects. First is the growing boy's recognition that he has a weak and puny frame, or that he is smaller than his brothers and pals. The second, in men of all ages, arises from the remarkable phenomenon of androgyny already mentioned. There is plenty of evidence for both of these biological inadequacies to be found in the foregoing biographies. Especially does it seem that unconscious awareness of the feminine component may be a stimulus to the overexploitation of their virility which is so characteristic of ulcer bearers. Indeed it may be said that a man who possesses that degree of femaleness which threatens the authenticity of his essential maleness becomes subject to deep-rooted unwitting fears lest he fail to play successfully the masculine rôle in life. This may be called the basic male fear. In connection with it one may refer again to Cannon's [4] original observation that it was the male cats which exhibited digestion-inhibiting effects perhaps owing to appropriately masculine resentment at being tied down on the operating board. The digestive movements of the female animals were not disturbed.

It may be said, further, that there are two phases of the survival problem which present themselves to man. One of these, his position in space, is a matter determined by the coöperation of bones, joints, spinal nervous system, striated muscle, conscious perception, discrimination, choice, and volition. Reactions in this phase are observed as outward conduct and determine his life of relation with the physical environment. The other aspect, that of the inner life of existence and procreation, is governed by the coöperating agencies of smooth muscle, uninfluenced by volition, the hypothalamic-autonomic system and the emotional reservoirs, whatever they may be. Consequently the whole vital mechanism reacts to fear stimuli from both outer and inner environment.

It is known that if the stimulus origin lies in the outer world the autonomic-smooth muscle-endocrine complex operates to prepare the creature for a vigorous coördinated physical response. This should normally terminate in the powerful, consciously directed conduct of fighting or running away. If the fear stimulus, however, should flow from the waking phantasy-world or the dream, confusion, indecision, and futile incoördination of the whole man supervenes. Under such circumstances there is no reality menace from which to flee or upon which to direct an attack. Nevertheless, notwithstanding the absence of an outer target, the defense mechanism has been emphatically mobilized and the individual inwardly senses its psycho-physiological tension.

Studies in psychobiology have shown that in the struggle to meet a given menace conflicts may arise between the phase which controls outer conduct

and that which directs inner. Such conflicts rest upon the fact that man displays intenser feeling states and greater physiological disturbance when the dangers menace his idealized ego rather than his body. In war, men go over the top with fear of wounds and death in their hearts, but still they send their bodies forward while the gastrointestinal tract runs away. It was well said by Henry of Navarre as he charged into battle: "Body, you're trembling, but if you knew where I was about to take you, you would tremble indeed!" And that is the daily self-imposed task of the ulcer-bearing male.

In this connection the question has lately been raised in England [5, 6, 7, 8] whether or not what seems to some observers to be an increase in peptic ulcer is due to stress of war. The figures from several sources are somewhat conflicting so that as yet no positive deductions can be drawn. However, it is now quite impossible to make comparisons between Army and civilian groups so far as exposure to danger is concerned. Moreover in two or three of our cases who went through frontal conditions in the last war, stomach symptoms were notably absent during the combat periods. Ulcers seem to reflect disturbance in the inner rather than the outer world.

It may be questioned, however, whether episodes which concern self-preservation in man are more disturbing than those involving his companion instinct of self-perpetuation. Indeed, the sex problem may, in the present stage of his evolution at least, hold greater dangers for him than the other. There can be no doubt that the energy of those psychobiological forces involved in reproduction is equal in man to that which exists in all animal forms. Consequently, whether for good or evil, the restraint upon it which customs of groping civilizations have required, gives rise to conflict within the consciousness of the individual. In a curious way this conflict of social law and biological necessity actually converts sex problems into fear problems. Any infringement of a taboo concerning the relationship of the sexes at once exposes the offender to his own or public criticism. The sufferings which flow from the patient's sense of guilt in these circumstances are no less terrible forms of punishment than those imposed arbitrarily upon the sex miscreant by a society still trembling under the Church's despotism of fear. And at that point the dial which indicates the source of disease producing emotional disturbance swings again to rest with its needle pointing out a menace, not to life perhaps, but to the important ego. Fear promptly surges through the individual and all the complicated mechanism for defense and attack is set in motion. To the end of total self-preservation, then, we can accept fear as the master emotion. In man it emerges with equal speed and intensity at threats from either the outer world of reality or that inner one which is composed of physiological and emotional forces. Laymen are more familiar with the latter under the name of conscience, "which makes cowards of us all."

It is difficult to review the records of individual reaction or reflex conduct of the digestive system which have been presented without recognizing that

emotional crises are correlated with stomach symptoms quite as clearly as are "dietary indiscretions." Indeed one is reminded of what every mother and pediatrician knows; that after an outburst of anger, or the experience of fright, infants and very young children may refuse food, vomit, or have diarrhea. In ulcer-bearing persons whose capacity for food reception is easily disturbed one sees again Nature's purpose of providing the infant with security at meal time. It is a simple thesis because deprivation of nutriment is the chief menace to the infant's life.

Instinctively, following the severance of the umbilical cord, the baby seeks the breast in his effort to reëstablish the food line as promptly as possible. Consequently the focus of its urgent demand is directed upon the mother who actually is its only source of nourishment. During the next six or seven years as other and varied hazards to safety increase with awakening consciousness and the complications of ever widening environment and social relationship, the child still finds in the mother its surest guarantee of security against them. Thus, with the first gulp of maternal milk, there is formed a mutual life-saving and perpetuating relationship—the child's life and the mother's immortality through her offspring—which remains by force of habit almost indestructible throughout the lives of both. This relationship, however, appropriate and significant as it may be in the early months and years when the mother's ego perpetuation urge and the infant's very life jointly hang upon it, can easily become a destructive force for both at a later time when each is fully capable of negotiating life independently as nature demands. In the mother's case the evil effects are expressed in exacting homage and exerting selfish power control; in the case of the son or daughter, the infantile emotional structure, retarded and ensnared within the offspring's adult frame and intellect, obstructs vigorous and independent action of the whole organism. Thus crippled it moves through life beneath a pall of free floating apprehension afraid of its own shadow when glimpsed alone and unaccompanied by that of its protectress.

As far as the infant of a day or a month, or even a year old, is concerned, his reliance upon the mother is quite impersonal. In his conditioned emotional patterns she represents only the means of survival, not a recognized personality. Later on the mother inevitably assumes an intensely personal and often demanding outward relationship from which the maternal significance as means of survival may disappear entirely. Indeed she may die or descend upon her offspring for support when they are still very young. Too often her ruthless control forms a menace to her children. In the unconscious levels, however, she continues to stand as the symbol of her primary function. Therefore, the mother principle carries on throughout life, clothed in many guises. Table 2 shows a grouping of these possible symbolic representations.

When one reads the routine histories of many cases of gastric or duodenal ulcer one is struck with the reiteration of the fact that the stomach is

sick and consequently has difficulty with strong foods. That basic thesis has determined the obvious existing therapy, namely, treat the sick stomach gently as you would the delicate digestive organ of the infant. It is also common experience that many cases have repeated hospital admissions and form a long line of "follow-ups" in the out-patient department. Almost without exception the records of these multiple visits repeat comment upon whether or not the patient has coöperated in carrying out his dietary regulations. Indeed the physician often sounds a note not unlike that of an irritated school ma'am whose recalcitrant pupil has failed to do his homework. When you read the intimate histories of persons who have ulcers, however, the impression develops that these individuals, like frightened neglected children, are striving continually to recapture and maintain the mother principle which had ministered so meticulously to the demands of that delicate infant receptacle for milk.

The more one observes these victims of chronic fear, often highly intelligent, futilely dynamic and over-striving people, the more one is forced to see

TABLE II

Mother Principle
or
Means of Survival

I. Own Mother:—
II. Surrogates: Foster mother, grandmother, wife, daughter, sister, nurse, doctor
III. Symbols: Social group ("I belong")
Business firm, job
School, college (Alma Mater)
Church, brotherhoods, masons, etc.
Inherited money, money in general
Food and housing
Hospital

in them supporting evidence for the notions concerning "Body Image" advanced by Schilder,[9] Coghill,[10] Bruch [11] and others. These authors concur in the belief that our bodies, indeed our whole personalities, have grown into images to ourselves of what we believe ourselves to be. "This image is built up in ourselves," writes Schilder, "in accordance with our instinctive attitudes;" while Coghill, the embryologist, considers man as "a mechanism which within the limitations of life, sensitivity and growth is creating and operating himself." Moreover, as Bruch points out, obese children, whose problem also is largely a food problem, derive security satisfaction from the static fact of size alone. Our observations would seem to indicate that the peptic ulcer patient in his form and conduct is the very antithesis to this. His best hope for security seems to lie in eager effort, however futile or poorly directed, to recapture the conditions earlier provided by the maternal protectorate. And so his linear, streamlined body forms the most appropriate symbolization of the striving for complete virility.

Conclusions

From the correlated experience of experimental alimentary physiology, human psychology and the clinic, one may reasonably assert that the symptoms and perhaps also the lesions of peptic ulcer are associated with psychic traumata as definitely as with inappropriate food. Indeed it looks almost as though the food factor were secondary. From the patient's point of view, however, the obviousness of the relationship between what he eats and what he feels forces his own and his physician's chief attention upon food. As a result, it is exceedingly difficult to interest or persuade the patient, and occasionally also the doctor, that his malady may be other than a feeding one. The best proof of this is that even today the routine treatment of peptic ulcer in good hospitals and private offices revolves almost exclusively about the stomach itself. There are, of course, admonitions "not to worry" and to "take it easy." But these are not often specific nor persistently followed.

The latter point clearly leads to the difficult question of psychotherapy in peptic ulcer. Full discussion of this still controversial matter cannot be undertaken here. It may be said, however, that by and large neither deep nor simpler forms of psychotherapy have as yet produced striking results. Some individual cases have been helped, others have failed to respond at all. In this respect, the problem may not be unlike that recently discussed by J. D. Southerland [12] in his report of 100 cases of war neuroses. He develops the notion that certain personality weaknesses may be analogous to many organic ones which cannot be radically altered. If one accepts the notion that an ulcer-bearer's emotional pattern is a correlate of his other constitutional components one cannot expect to achieve much alteration of it. Careful study of the person, however, at least offers the possibility of discovering his reaction type and capacity and so assist in evaluating the degree and nature of environmental stress to which he can adjust.

In the treatment of the ulcer itself measures must be established to combat hyperacidity either by chemical means or by the selection of bland protein foods or milk. The psychological import of the latter is obviously to reëstablish the expectations of the infant digestive organ. The basic view of ulcer here presented, however, assumes the organism's effort not to depart from, and if possible even in adulthood, to regress to the protectorate of the mother principle. Indeed it appears as though the psychological panel of the ulcer patient had failed to mature. It is for this reason that because of their symbolic effects bed rest and frequent small feedings of milk, tendered by a nurse, come into question. While such a plan may ease local distress it can also, by virtue of its symbolic content, obstruct reëstablishment of self-sufficiency and self-respect. Meulengracht's [13] remarkably successful feeding of regular diets, with meat, in severe cases, even bleeding ones, would seem to support this thesis.

The views expressed in this paper consequently lead to the following suggestions for a reorientation of the present routine management of the

peptic ulcer problem. They are based on the belief that " 'tis not the stomach but the man who's ill."

1. Only cases of severe hemorrhage and perforation to be admitted as ward patients. At that stage such cases are emergency medical or surgical problems, like any other digestive tract accident of the sort.

2. All other cases of peptic ulcer to be handled in the outpatient department.

3. At the first interview an effort should be made to discover specific emotional traumata and the nature of the patient's individual reaction to them rather than maximum recording of dietetic indiscretions. In regard to the former, the object is not to record a hard luck story and the adverse environment. The nature of the patient's emotional response is the issue.

4. Return appointments at short intervals for three or four interviews. During these the patient may be helped to the realization of how much he himself has to do with his own malady. Every effort to encourage self-respect and self-reliance is desirable, but it is usually difficult to alter the actual outside situation of a patient's life. Moreover, it is always a question how much a patient should be helped directly by the physician and how much he should be required to do for himself. Too much help tends to encourage the patient's unconscious effort to regress toward infancy.

5. Antacid drugs may be used, but minimal emphasis on infant feeding and maximal on the establishment of adult fare is called for, even at the cost of slight discomfort.

6. Before discharge following gastrectomy or operation for perforation, the patient should be turned over to the medical psychiatrist for reëducation planned to wean him from the mother principle and to reëstablish his self-respect.

7. The cure of peptic ulcer probably must be looked for through the inversion of those regressive psychobiological forces which engender it rather than by local treatment of the lesion itself.

8. Peptic ulcer may turn out to be one of those widespread human afflictions which, like tuberculosis and cancer, can be controlled to a considerable extent by popular education directed at prevention through understanding.

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SULFADIAZINE; A STUDY OF ITS EFFECT ON HEMOLYTIC STREPTOCOCCI *

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IN view of the fact that patients with hemolytic streptococcal infections who are treated with sulfanilamide often continue to have a prolonged and protracted illness, it is desirable to search for more effective chemotherapeutic agents. Recently, another sulfonamide derivative, sulfadiazine, has been described by Roblin, Williams, Winnek, and English.[1] In preliminary studies it was found to protect mice against hemolytic streptococcal and pneumococcal infections.[2] Later,[3] it was reported that it was superior to either sulfanilamide or sulfapyridine in the treatment of experimental infections of mice due to the hemolytic streptococcus. It was pointed out that the animals receiving sulfadiazine had a higher and more prolonged concentration of the drug in the blood and, therefore, the increased number of survivals in the infected mice might have been due to these factors.[3]

In man, the administration of sulfadiazine is followed by very few toxic effects. A recent report by Peterson, Strauss, Taylor, and Finland [4] on the absorption, excretion, and distribution of sulfadiazine in tissues shows that it is absorbed readily from the gastrointestinal tract, and higher concentrations in the blood are reached and sustained longer than with sulfanilamide, sulfapyridine, or sulfathiazole. The conjugation of the drug is usually slight and there is no tendency for the drug to be retained in the body. Neither sodium sulfadiazine nor sulfadiazine was absorbed to any appreciable extent from the rectum. It will diffuse from the blood to the pleural or ascitic fluid and into the subarachnoid space in amounts varying from 50 to 94 per cent of the level in the blood. It was also noted by them that there was less nausea, vomiting, and mental depression following the use of this drug than exists following the other sulfonamides. These results are in agreement with those obtained by Sadusk and Tredway [5] and Reinhold, Flippin, Schwartz, and Domm.[6]

The present study was undertaken to assess the relative activity of sulfadiazine and sulfanilamide against hemolytic streptococci in whole blood of normal individuals. We were also interested to obtain information concerning the concentration of sulfadiazine which produces a maximal effect.

METHODS

The methods of investigation were the same as we have described previously.[7] Defibrinated whole blood from normal individuals was used

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for media. The various drugs were added in vitro and the concentration determined by chemical analysis.[5] In some of the experiments the drug was given by mouth, and samples of blood were withdrawn one, three, and four hours later. Determination of the concentration of the drug was then made on these samples.

In all, five different strains of hemolytic streptococci were used; three strains were isolated from the blood of patients with bacteremia, and two were isolated from the nasopharynx. They all showed beta hemolysis on blood agar plates and belonged to Lancefield's Group A. The organisms were stored on blood agar slants and a 12-hour peptone broth culture was used for the inoculations.

One-tenth c.c. of various saline dilutions of the test organism was added to 0.5 c.c. of the defibrinated blood containing varying concentrations of drug. Eight different dilutions of organisms were added to each sample of blood. The tubes were then sealed and rotated in the incubator for 24 hours. The contents of the tubes showing no hemolysis were plated out and the colonies counted. In those tubes showing hemolysis the number of organisms present varied between 10^{-7} and 10^{-8} per c.c.

Effect on the Killing Power of Whole Blood Following Administration of Sulfadiazine by Mouth

In these experiments samples of blood were withdrawn before and three hours after the administration of 4 gm. of sulfadiazine by mouth. These two samples of blood were then used as culture media as described above.

Thirty experiments were performed; table 1 shows the results of five

Table I

Effect of Sulfadiazine on Whole Blood after Its Administration by Mouth to Normal Individuals

Strain	Culture Media	Dilution of Culture						
		10^1	10^2	10^3	10^4	10^5	10^6	10^{8}†
F	Whole blood	+*	+	+	+	+	0	2
	Whole blood plus S.D. 6.2 mg. per 100 c.c.	2	0	0	0	0	0	
98	Whole blood	+	+	+	+	+	0	2
	Whole blood plus S.D. 4.8 mg. per 100 c.c.	13	0	0	0	0	0	
K	Whole blood	+	+	+	+	+	0	3
	Whole blood plus S.D. 2.6 mg. per 100 c.c.	0	1	0	0	0	0	
98	Whole blood	+	+	+	+	+	+	2
	Whole blood plus S.D. 2.6 mg. per 100 c.c.	16	0	0	0	0	0	
B	Whole blood	+	+	+	+	6	10	1
	Whole blood plus S.D. 10 mg. per 100 c.c.	0	0	0	0	0	0	

* Hemolysis of blood indicates 10–100 million organisms per c.c.
† Total number of organisms inoculated into 10^6 dilution.

such experiments which are typical examples of the group as a whole. The concentration of free sulfadiazine in the blood varied from 2.6 to 10 mg. per 100 c.c. In every instance a bactericidal effect was observed. From these results it was clear that administration of sulfadiazine by mouth to normal individuals increased the bactericidal action of normal blood against hemolytic streptococci. This is in striking contrast to our previous studies with sulfanilamide,[8] in which a bactericidal effect was observed only when natural antibodies were present, or when a very small number of organisms was used in the inoculum.

In figure 1, the results of giving a single dose of 5 grams of sulfadiazine by mouth to three normal individuals are shown. The bactericidal power

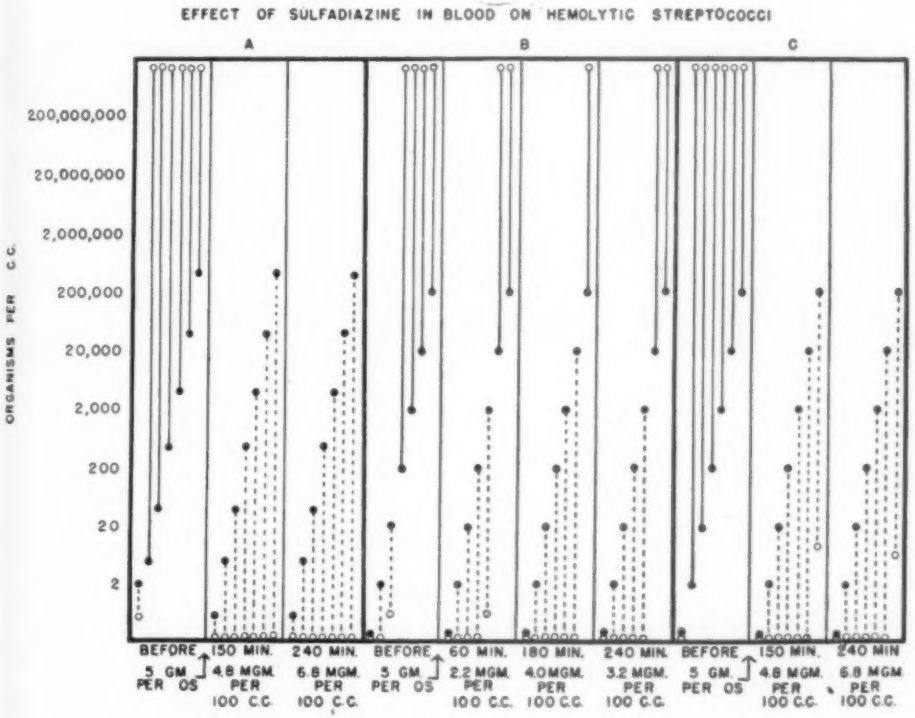

FIG. 1. The solid dots indicate the number of organisms in the inoculum, the circles, the number of organisms after 24 hours' incubation.

of the blood was tested before the exhibition of the drug, and then at varying periods of time blood was obtained for chemical and bactericidal tests. In all three individuals a bactericidal effect was observed when sulfadiazine was present in concentrations varying from 2.2 to 6.8 mg. per 100 c.c. These experiments show that sulfadiazine increases the bactericidal power of the blood against the hemolytic streptococcus when it is given by mouth.

Effect of Varying Concentrations of Sulfadiazine in Blood Following Oral Administration

We then determined the concentration of drug which would produce the maximal effect. Figure 2 shows the results obtained in 10 normal individuals. In these experiments blood was withdrawn before sulfadiazine was administered and at varying intervals thereafter. All samples of blood were stored in the icebox until the last specimen was taken.

The concentration of free sulfadiazine in the blood varied from 0.8 mg. per 100 c.c. to 10 mg. per 100 c.c. In the blood sample containing 0.8 mg. per 100 c.c. there was a definite increase in the killing power. When

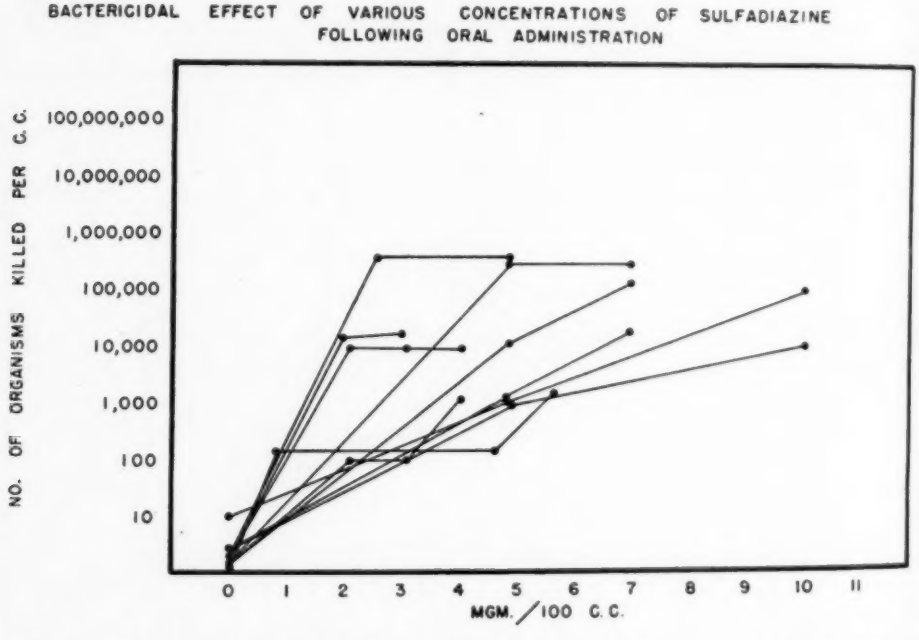

Fig. 2. Solid dots represent number of organisms present after 24 hours' incubation.

the concentration was raised to 5.6 mg. per 100 c.c., a greater increase in the killing power was observed. These experiments demonstrate, then, that as the concentration of sulfadiazine in the blood is increased there is an associated increase in the bactericidal power of the blood against the hemolytic streptococcus. Maximal effects were observed when a concentration of 4 to 5 mg. per 100 c.c. or higher was obtained.

A comparison of the bactericidal power of a sample of whole blood containing specific antibody and one without any antibody following the addition of sulfadiazine is shown in figure 3. It is plain that sample A exhibited a marked bactericidal action.

When the concentration of sulfadiazine was 3 mg. per 100 c.c., 1,800,000

hemolytic streptococci per cubic centimeter of blood were killed. In sample B, which contained no antibody, only 1,000 organisms were killed when the concentration was 4 mg. per 100 c.c. This striking difference was due to the presence of antibody in one specimen of blood and its absence in the other. It is seen, then, that sulfadiazine greatly enhances the bactericidal effect of whole blood containing antibody and that this is evident even when low concentrations of the drug are used.

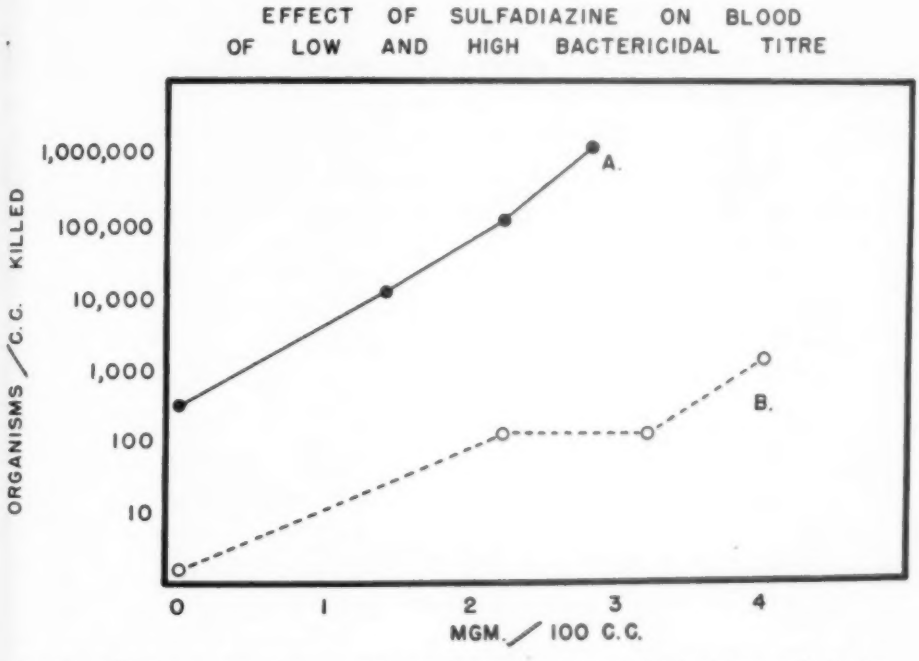

FIG. 3. Blood A is the sample in which 600 organisms were killed without sulfadiazine.

COMPARATIVE EFFECT OF SULFANILAMIDE AND SULFADIAZINE WHEN ADDED TO WHOLE BLOOD IN VITRO

Inasmuch as it was demonstrated that sulfadiazine was bactericidal for the hemolytic streptococcus, we then turned our attention to the study of the relative merits of sulfanilamide and sulfadiazine in whole blood. The following procedures were carried out.

Blood was obtained in 150 c.c. amounts from normal individuals and defibrinated. To two 24 c.c. samples of this blood 5 mg. of powdered sulfadiazine and sulfanilamide respectively were added and thoroughly mixed for one hour. These two samples were then diluted with the blood so that varying concentrations of drug were obtained. These concentrations were then checked by chemical analysis. Eight dilutions of the test organism were added to each concentration of blood containing the two drugs. After

24 hours' incubation the number of organisms was determined as outlined above.

Figure 4 shows the results obtained in one of these experiments. When the original inoculum was 240,000 organisms per cubic centimeter of blood, the growth of organisms was not affected by either sulfanilamide or sulfadiazine until the concentration of the drug was above 10 mg. per 100 c.c. At the higher concentrations there was definite killing in the blood con-

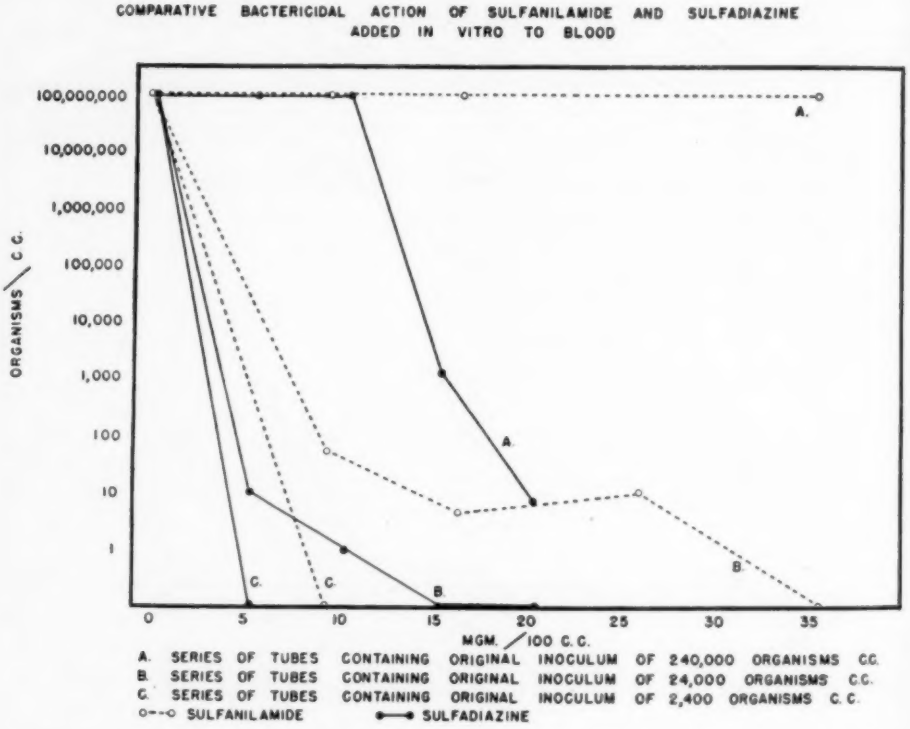

FIG. 4. Points represent the number of organisms per cubic centimeter present after 24 hours' incubation.

taining sulfadiazine (Experiment A). When small inocula were used, both the sulfanilamide and sulfadiazine-containing cultures exhibited a bactericidal action, although there was a tendency for the blood containing sulfadiazine to exhibit killing at lower concentrations (Experiments B and C).

COMMENT

From the above experiments it is plain that sulfadiazine is a powerful bactericidal agent when it is tested against hemolytic streptococci. This effect was demonstrated whether the drug was added directly to whole defibrinated blood in vitro or whether it was given by mouth. The bactericidal

effect was present in dilutions as low as 2 to 5 milligrams per 100 c.c., and it was enhanced by the presence of natural or acquired antibodies. When the relative merits of sulfanilamide and sulfadiazine were compared in vitro, it was clear that sulfadiazine was always more effective in killing hemolytic streptococci.

The evidence at present is suggestive that sulfadiazine will be superior to sulfanilamide in the treatment of hemolytic streptococcal infections in man. Since it is relatively non-toxic and is readily absorbed from the gastrointestinal tract and diffuses into the serous sacs and meninges in high concentration, it would seem to be preferable to sulfanilamide in the treatment of hemolytic streptococcal infections.

Summary and Conclusions

1. Sulfadiazine is bactericidal for the hemolytic streptococcus when the inoculum is small and the concentration is between 2 and 5 mg. per 100 c.c.

2. Its action is enhanced by the presence of antibactericidal antibody, either natural or acquired.

3. When sulfadiazine is compared with sulfanilamide, it is found to be superior insofar as its bactericidal effect is concerned, and it is more effective as a bacteriostatic agent in lower dilutions.

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RESPONSE TO SULFAPYRIDINE IN 241 CASES OF PNEUMONIA, WITH ESPECIAL REFERENCE TO LACK OF PROMPT RESPONSE IN SOME CASES *

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This paper deals with a series of 241 unselected cases of pneumonia treated with sulfapyridine in 1938–1939 and 1939–1940. This group, although not numerically impressive, is reported because the patients were followed closely and studied carefully, and because an analysis of those cases in which sulfapyridine was not promptly effective yields hitherto unemphasized information of value.

Distribution of Cases

The cases reviewed total 241, and are consecutive and unselected save for the omission of a few that were admitted moribund and died within less than 24 hours after admission. Of the series, 73 were seen in the winter of 1938–1939, and 168 in the winter of 1939–1940. There were 129 males and 112 females. The age distribution of the group is shown in table 1. There were 21 deaths and 13 autopsies in the group, with a mortality rate of 8.7 per cent for the series.

Method of Treatment

In most of these cases treatment with sulfapyridine was started within four days of the onset of the pneumonia. All of the patients except a few very young infants had an initial blood culture before chemotherapy was started, and if the initial blood culture was positive, blood cultures were repeated daily until they were repeatedly negative. Sputum was studied by the Neufeld technic and culturally, by the injection of mice and the subsequent Neufeld examination of the peritoneal exudate if the pneumococci originally found were not typable with the Neufeld quellung reaction.

The usual oral dosage of sulfapyridine for adults was an initial dose of 2 or 3 gm., then 1 gm. every four hours for two days, and then 1 gm. every four hours, with gradual reduction of the dose, until it was discontinued after the temperature had remained normal for five days. In children the dose was correspondingly smaller, averaging 1½ grains per pound of body weight in 24 hours, after an initial dose of about one-half the calculated daily total. In children the drug was stopped after the temperature had remained normal for two days. Bicarbonate of soda was given in amounts equal to the sulfapyridine. The concentration of the drug in the blood was determined daily

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From the Medical Service, Sinai Hospital, Baltimore.

for the first few days and then less frequently in most cases, with adjustment of the dosage if it was felt that the blood level was not high enough. In most cases the average concentration of total sulfapyridine (Marshall's method) in the blood was between 4 and 7 mg. per cent. All patients had daily urinalysis, daily estimation of hemoglobin and leukocyte and differential blood counts.

No effort was made to restrict the total fluid intake, fluids being forced to a high total daily intake in most cases.

TABLE I

Age Distribution of Cases and Deaths

Age (Years)	No. Cases	Deaths (Age)
Less than 1	22	7, 8, 8 (mos.)
1	16	12, 13, 13, 18, 18 (mos.)
2	7	
3	9	
4	4	
5	8	
6	9	
7	8	7 (yrs.)
8	4	
9	0	
10	2	
11	3	
12	1	
13	4	
14	4	14 (yrs.)
15	4	
16–20	11	
21–25	12	
26–30	10	
31–35	11	
36–40	13	
41–45	6	
46–50	8	
51–55	12	55 (yrs.)
56–60	14	59, 60 (yrs.)
61–65	11	62 (yrs.)
66–70	18	67, 67, 69 (yrs.)
71–75	5	71 (yrs.)
76–80	5	77, 78, 79 (yrs.)
Totals	241 Cases	21 Deaths

RESPONSE TO SULFAPYRIDINE

Of the 241 cases treated, 21 died and 220 recovered. Most of the patients who recovered responded with a drop of temperature to a normal level, subsequently maintained, within 48 hours after administration of sulfapyridine was started. We shall refer to this group as those responding by "crisis." There were 173 in this "crisis" group. The remaining 47 cases showed no such dramatic drop of temperature, and seemed not to respond to the chemotherapy. This latter group will be referred to as the "lysis" group. In this paper we are interested chiefly in an analysis of the "lysis" group, in order to discover why these 47 cases did not respond to treatment promptly or at all.

1. Distribution of the Pneumonia. The cases were classified as either lobar pneumonia or bronchopneumonia, depending upon whether the physical signs were those of massive or of patchy consolidation and upon the roentgen-rays which were taken in many cases. According to this classification, which is admittedly arbitrary, the cases were distributed as follows:

Response	Distribution of Pneumonia		Total
	Lobar	Broncho-	
Crisis	94	79	173
Lysis	12	35	47
Total	106	114	220

It is seen that failure to respond promptly was much more frequent among the cases with patchy involvement than in those with true lobar consolidation. And again, of those failing to respond promptly only one-fourth had true lobar involvement, other factors being equal. In most cases the number of lobes involved was apparently not directly related to response to sulfapyridine.

2. Etiology of the Pneumonia. It was thought that the failure to respond to treatment might be due not so much to the type of anatomical distribution as to the different bacteria responsible for the lobar or the bronchopneumonia. The cases were, therefore, classified according to etiology and response to treatment as follows:

Sputum	Termination by		
	Lysis	Crisis	Deaths
Typable pneumococci	15	68	11
Pneumococci of no known type	3	30	—
Pneumococci—Strep.	—	4	—
Pneumo.—Staph.—Strep.	3	17	2
Pneumo.—Staph.	6	22	2
Staph. predominating—few Pneumo.	7	2	—
Staphylococci	7	10	2
Beta Streptococci	2	2	—
Strep.—Staph.	4	14	3
Sputum not obtained	—	4	1
Totals	47	173	21

A study of this chart shows that if the predominating organism in the sputum was the pneumococcus (168 cases), most of the patients responded promptly to treatment (crisis, 141; lysis, 27); but if staphylococci or streptococci predominated (52 cases), a greater proportion did not respond promptly to sulfapyridine (crisis, 32; lysis, 20).

3. Complications. The cases that did not respond promptly to treatment were studied to ascertain the possible effect of the presence of complications upon the response to chemotherapy, with the following results:

Complication	Lobar	Lysis Broncho-
Spread	1	1
Bacteremia	2	1
Marked pleurisy	1	—
Pleural effusion	2	2
Empyema	2	—
Unresolved pneumonia	—	1
Otitis media	—	3
Mastoiditis	—	2
Severe nausea and vomiting	—	3
Drug rash	1	1
Hematuria	1	2
Toxic neuritis	—	1
Totals	10	17

Thus, of 12 cases of lobar pneumonia which did not respond promptly, 10 had complications as listed; of 35 cases of bronchopneumonia which did not respond promptly, 17 had complications. In this series complications were more frequent among the cases of lobar pneumonia which did not respond than among the cases of bronchopneumonia which did not respond.

Complications of Sulfapyridine Therapy

Nausea and vomiting occurred frequently after the administration of sulfapyridine, but in only a small number of cases were they severe enough to necessitate discontinuing the use of the drug. Other complications met with in this series were:

Complications	No. Cases
Drug rash	4
Microscopic hematuria	8
Gross hematuria	6
Gross hematuria, with abdominal pains	1
Moderate hemolytic anemia	2
Marked drop in total WBC	
To 5000 cells	1
To 4000 cells	1
To 1600 cells	1
Toxic neuritis	1
Total	25

None of the complications listed deserves particular consideration except perhaps a toxic neuritis that developed. This occurred in a 29 year old white male with Type III bronchopneumonia. His temperature fell gradually after the administration of sulfapyridine was started, reaching a normal level six days later. During convalescence he showed signs of a neuritis of the terminal filaments of the right ulnar and musculocutaneous nerves. This improved gradually but was still present at the time of his discharge.

Complications of Pneumonia

The complications met with in this series total 30, consisting of 16 cases of otitis media, three cases of mastoiditis, nine cases of pleural effusion and two cases of empyema.

1. Otitis Media. Of the 16 cases of otitis media, nine were present on admission and seven were noted later. Most of these required myringotomy. Response to sulfapyridine was prompt in 12 cases. The presence of otitis was apparently not related to the duration of the disease on admission, nor to the blood sulfapyridine level. Practically all of the cases occurred in children, and in only one case was there a typable pneumococcus in the sputum —Type XXII. The aural discharge contained hemolytic *Staphylococcus albus* or *aureus* in most cases, except for one case in which a few streptococci were also present.

2. Mastoiditis. Mastoiditis occurred in three infants, aged 8 months, 9½ months, and 18 months, respectively. In only one case was response to sulfapyridine prompt. There was no apparent relation to the duration of the disease on admission, nor to the blood sulfapyridine level. Mastoidectomy was performed in all three cases, with recovery in all. The cultures from the mastoids at operation yielded hemolytic *Staphylococcus aureus* in two cases, and pneumococcus in one case.

3. Pleural Effusion. Of the nine cases of pleural effusion, four were noted on admission and five were discovered later. Thoracentesis was performed in six cases, and cultures of all of the fluids were sterile. There was prompt response to sulfapyridine in five of the nine cases. The sputum showed typable pneumococci in five cases: Types I, III, VII, VIII, XII. The ages of the patients were 6, 7, 16, 18, 29, 29, 33, 45, and 59 years, respectively. The presence of the pleural effusion was apparently not related to the duration of the disease on admission, nor to the blood sulfapyridine level.

4. Empyema. There were two cases of empyema among the 220 cases which recovered. One of these was in a 42 year old white female with Type II pneumonia involving the left lower lobe and right middle and lower lobes. Her blood culture at the time of admission showed one to three colonies Type II pneumococcus per c.c. This patient had a poor response to specific serum plus sulfapyridine (260,000 units on third and fourth days of disease). Blood sulfapyridine concentration reached 4.9 mg. per cent. Temperature fell in 18 hours and then rose again and remained elevated. Thoracentesis on the twelfth day yielded 10 c.c. of cloudy fluid which was sterile on culture. The next day the sulfapyridine was discontinued, and the blood sulfapyridine the following day was 1.0 mg. per cent. Thoracentesis on the seventeenth day yielded 90 c.c. of purulent fluid, containing Type II pneumococcus. The patient ran a high spiking temperature for several weeks, which subsided gradually following thoracotomy on the eighteenth day of the disease.

The second patient with empyema did not require operation. He was a 32 year old white man admitted on the fifth day of his disease with pneumonia of the left lower and right lower lobes. Sputum showed Type XXII pneumococcus. Repeated blood cultures were negative. Sulfapyridine treatment was started on admission, the blood level reaching 10 mg. per cent. Temperature gradually fell during the first five days of treatment, then rose on the eighth day, and sulfapyridine was discontinued. Temperature was normal by the thirteenth day after admission and remained so. On the fourth day after admission thoracentesis yielded 40 c.c. of cloudy fluid which contained Type XXII pneumococcus. This fluid became sterile later, as shown in the following table:

Day of Treatment	c.c.	Cells per cu. mm.	Culture	Sulfapyridine Conc. Mg. %	
				Blood	Pleural Fluid
4	40	1800 (L-24, P-76)	Type XXII		
6	15	1950 (L-19, P-81)	Sterile	8.3	6.2
7	200	1050 (L-36, P-64)	Sterile	10.0	7.1
9	20	2050 (L-22, P-78)	Sterile		
11	—	—— (————)	Sterile		

Bacteremia

In the entire series of 241 cases, there were 13 cases with bacteremia. Of these, three died, one developed empyema requiring thoracotomy, two had sterile pleural effusions, and one had delayed resolution. Three had a prompt response to sulfapyridine; nine showed a delayed response if any; and three died. The types of pneumococci found in the blood were Type I in four cases, Types II, III, XIV and XVIII in one case each, and Type VII in two cases.

Deaths

There were 21 deaths in the series of 241 patients treated with sulfapyridine, a mortality of 8.7 per cent for the group. The age distribution of these cases is shown in table 1. There were eight deaths in children under 18 months of age, and 11 deaths in adults 55 years of age or older, with only two deaths in the group between three and 55 years of age, i.e., mortality rates of 21.0 per cent, 16.9 per cent, and 1.4 per cent, respectively. The important findings in each of the fatal cases are summarized in table 2. Only two of the fatal cases occurred in patients who were not very young or very old. One of these was a seven year old child admitted late in the course of the disease, with Type XVIII pneumococcus in his sputum, pneumonia of the entire right lung on admission, and empyema on the right due to Beta hemolytic streptococci. The other was a 14 year old child with

TABLE II

Summary of Findings in Fatal Cases

No.	Age	Sputum	Remarks—Autopsy
1.	7 Mos.	Type XIV Pneumo.	224 Colonies per c.c. on admission blood culture. Bilateral otitis media on admission, yielding Beta hemolytic streptococcus. Given 2 c.c.Type XIV rabbit serum two hours before death on second hospital day. Autopsy: Lobar pneumonia, right lower lobe. Acute fibrino-purulent pleurisy, right, yielding Type XIV pneumococci on culture. Pleural effusion, right, small.
2.	8 Mos.	Type XXIX Pneumo.	Negative blood culture. Died on fifth day in hospital after initial crisis and afebrile period of two days. Received very small sulfapyridine dosage after first day of treatment. Autopsy: Pneumonia of all five lobes. Small amount fibrinopurulent pleurisy.
3.	8 Mos.	Type XXIII Pneumo.	No blood culture obtained. Admitted on third day of disease and died on following day. Cyanotic on admission. Autopsy: Heart blood sterile. Bilateral bronchopneumonia. Pleural effusion on right, 300 c.c. sero-sanguinous fluid. Pleura of both lungs normal. Culture of pleural fluid and of secretion in right bronchus yielded pure Alpha hemolytic streptococci.
4.	12 Mos.	Hem. strep. Non-hem. staph.	Blood culture sterile. Admitted with otitis media and malnutrition. Signs of pneumonia appeared on sixth day in hospital. Received 0.4 gm. sodium sulfapyridine intravenously, blood level reaching 10.1 mg. per cent. Died on seventh day in hospital. Autopsy: Lobar pneumonia, right and left lower lobes. Pleural effusion, bilateral. Acute serous mastoiditis, bilateral (streptococci cultured on right side).
5.	13 Mos.	Pneumo. Staph	Blood culture sterile. Admitted on second day of disease, received sulfapyridine immediately, concentration reaching 7.7 mg. per cent next day. Temperature dropped to normal within 24 hours after treatment was started. On second hospital day child died suddenly while being fed. Autopsy: Bronchopneumonia of entire right lung. Atelectasis of left lower lobe. Widespread congenital deformities of genitourinary system.
6.	13 Mos.	Pneumo. Staph. Strep.	Blood culture sterile. Admitted on first day of disease, treatment with sulfapyridine started immediately. Blood level not obtained. Initial drop in temperature, rising again irregularly to 107° and 108° F. at death on third hospital day. Had recovered from mumps two weeks before. Autopsy: Acute bilateral lobular pneumonia involving all lobes, especially right upper lobe. Pleura normal. Postmortem pleural and lung culture yielded *Staphylococcus albus* and *B. pyocyaneus*.
7.	18 Mos.	Not obtained	Blood culture and sputum not obtained. Admitted and treatment started on fourth day of disease, blood level of 6.5 mg. per cent sulfapyridine reached. Bronchopneumonia of left upper and left lower lobes. No response to sulfapyridine, with gradual downward course. Thoracentesis (left) on second hospital day yielded small amount of fluid which yielded hemolytic *Staphylococcus aureus* in culture. Child died on fourth day in hospital. No autopsy.

TABLE II—*Continued*

No autopsy.

TABLE II—*Continued*

No.	Age	Sputum	Remarks—Autopsy
8.	18 Mos.	Pneumo. Few staph.	Admitted with influenzal meningitis of 2 to 3 days' duration. Small areas of bronchopneumonia noted. Received 20 c.c. of anti-influenzal serum. Also received sulfapyridine orally and sodium sulfapyridine intravenously, the latter being followed by convulsions for 8 hours, yielding only to ether. No response to treatment. Autopsy: Acute purulent meningitis, yielding *Hemophilus influenzae* in culture. Bilateral bronchopneumonia.
9.	7 Yrs.	Type XVIII Pneumo.	Admitted moribund after illness of 2 weeks at home, treated inadequately at home with sulfapyridine (blood level too low to read on admission). Blood culture sterile, with pneumonia of entire right lung on admission. Empyema, right, on admission, yielding Beta hemolytic streptococci in culture. Received sulfapyridine and intravenous sulfanilamide. Course steadily downward, patient dying 36 hours after admission.
10.	14 Yrs.	Hem. *Staph. aureus*	Admitted on second day of disease with involvement of right lower lobe, very toxic. Received sulfapyridine orally and intravenously, blood level reaching 14.3 mg. per cent. No response to treatment, dying day after admission Postmortem lung puncture fluid yielded no pneumococci on mouse injection; showed great numbers of staphylococci on smear.
11.	55 Yrs.	Pneumo. Non-hem. staph.	Bronchopneumonia left lower lobe on admission on fifth day of disease, received sulfapyridine immediately, level of 9.1 mg. per cent reached. Temperature became normal on fourth day for 24 hours, then rose coincident with signs of spread to more of left lung and to right base. Died on sixth hospital day. Diabetic hypertensive with cardiac enlargement, azotemia, anginal syndrome.
12.	59 Yrs.	Strep. Staph. Few Pneumo.	Blood culture sterile. Admitted on second day of disease, received sulfapyridine immediately, blood level of 4.4 mg. per cent reached. No response to drug. Hypertensive with cardiac enlargement. Died on fifth hospital day. Autopsy: Pleural effusion, left, 1000 c.c., watery, sanguinous. Right effusion 100 c.c.
13.	60 Yrs.	Type III Pneumo.	Blood culture sterile. Admitted on second day, given sulfapyridine, blood level not obtained. Bronchopneumonia both bases. Initial fall in temperature, which promptly rose again, together with rise in blood sugar to 400 mg. per cent despite increase in insulin. Died after two days in hospital. Diabetic. Positive Wassermann. Arteriosclerotic cardiovascular disease. Several previous attacks Type III pneumonia.
14.	62 Yrs.	Type I Pneumo.	Admission blood culture 2000 colonies per c.c. Admitted on sixth day of disease, sulfapyridine started immediately, blood level of 5.3 mg. per cent reached. Died 36 hours after admission. Autopsy: Pneumonia of all five lobes.
15.	67 Yrs.	Type I Pneumo.	Blood culture sterile. Admitted on seventh day of disease, treatment started, blood level of 3.2 mg. per cent obtained. Toxic, cyanotic on admission. Given 120,000 units Type I horse serum day after admission. No response. Died day after admission. Autopsy: Lobar pneumonia, left upper lobe. Acute fibrinous pleurisy, left. Aortic stenosis and insufficiency due to arteriosclerosis. Chronic miliary tuberculosis of both lungs, adrenals, mediastinal, hilar and tracheobronchial lymph glands.

TABLE II—*Continued*

No.	Age	Sputum	Remarks—Autopsy
16.	67 Yrs.	Type XIX Pneumo.	Blood culture sterile. Admitted on first day of disease with pneumonia and meningitis and otitis. Received sulfapyridine, concentration in blood reaching 8.7 mg. per cent, and 300,000 units Type XIX horse serum. Course downward, dying three days after admission. Type XIX pneumococcus cultured from ear, spinal fluid, and postmortem lung. Autopsy: Lobar pneumonia, left lower. Acute fibrinous pleurisy, left. Acute purulent meningitis. Carcinoma left breast. Arteriosclerotic heart disease.
17.	69 Yrs.	Type III Pneumo.	Blood culture in broth yielded Type III pneumococcus on admission. Duration of disease unknown, with pneumonia of left upper and lower lobes on admission. Blood sulfapyridine level 7.6 mg. per cent. Initial response with later rise in temperature, and increasing cardiac embarrassment. Died on fourth hospital day. Decompensated arteriosclerotic cardiovascular disease, with azotemia.
18.	71 Yrs.	Type XI Pneumo.	Blood culture sterile. Pneumonia both lower lobes on admission on second day of disease. Initial response to sulfapyridine with blood level of 5.7 mg. per cent. Pneumonia spread and temperature rose as sulfapyridine dose was reduced and concentration became too low to read on fifth hospital day. Died on ninth day in hospital. Arteriosclerotic and hypertensive cardiovascular disease.
19.	77 Yrs.	Hem. *Staph. aureus* Few strep.	Treatment started on admission on seventh day of disease, with prompt drop in temperature. Temperature rose again after being normal 8 days; but this time there was no response to sulfapyridine, temperature gradually falling after 5 more days. A third time the temperature rose, spiked, and did not respond at all to sulfapyridine. Bronchoscopy during third febrile episode showed congested mucosa. Autopsy: Bronchopneumonia right lower lobe. Bronchiectasis with many cavities, both lower lobes, right upper lobe. Pulmonary tuberculosis, inactive. Marked pleural and pericardial adhesions. Arteriosclerotic kidney disease.
20.	78 Yrs.	Type III Pneumo.	Blood culture sterile. Admitted on fourth day of disease, sulfapyridine started immediately, blood level of 10.2 mg. per cent reached. Initial drop of temperature to normal in 48 hours, then rose again, patient dying on twelfth day of disease. Autopsy: Pneumonia right upper and lower lobes, left lower lobe. Alcoholic cirrhosis of liver, coronary sclerosis, myocardial scars, arteriosclerotic nephrosclerosis.
21.	79 Yrs.	Staph. Strep. Pneumo.	Blood culture sterile. Admitted on fifth day, treatment started, and blood level of 5.2 mg. per cent reached, with temperature dropping to normal within 36 hours. Bronchopneumonia of both bases. Temperature remained normal, and patient died suddenly in pulmonary edema on ninth day in hospital after being up one day. Arteriosclerotic cardiovascular disease.

probably staphylococcal pneumonia of the right lower lobe, admitted on the second day of the disease and dying the following day.

Summary

1. The results of the treatment of a series of 241 cases of pneumonia with sulfapyridine with 21 deaths have been recorded and analyzed.

2. An attempt has been made to explain the failure of some cases to respond promptly to sulfapyridine.

3. The data emphasize the value of the drug in the treatment of pneumococcal pneumonia and indicate some of the hazards incident to its administration.

THE CARDIOVASCULAR ASPECTS OF CAROTID SINUS HYPERSENSITIVITY WITH SPECIAL REFERENCE TO SOME CARDIAC ARRHYTHMIAS *

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The effects of carotid sinus hypersensitivity on the cardio-vascular system are well known.[1, 2] Most of the case records are concerned with patients who had a basic normal sinus rhythm whereas only a limited number of reports could be found wherein carotid sinus hypersensitivity was associated with cardiac arrhythmia. Weiss and Baker [1] reported one case with auricular fibrillation (in this patient carotid sinus stimulation produced only slight slowing of the ventricular rate) and Hiatt and Adams [3] published the record of one patient with auricular flutter. A survey of the literature failed to reveal the association of paroxysmal tachycardia and carotid sinus hypersensitivity.

Recently the opportunity was presented to observe four instances of carotid sinus hypersensitivity, each occurring in a different cardiac rhythm, viz: regular sinus rhythm, paroxysmal auricular tachycardia, auricular fibrillation and auricular flutter. It is interesting to note that these four cases were first seen at the New York Post-Graduate Hospital within a period of two weeks.

Case 1. A 58-year-old Jewish dressmaker was admitted to the New York Post-Graduate Hospital on April 1, 1940 on the service of Dr. John D. Currence. Two weeks prior to admission the patient had what he described as an "upset stomach." At that time he had a large meal following which he felt bloated. He took some salts and almost immediately felt dizzy and vomited. This was followed by a feeling of generalized warmth and subsequent relief. He felt well for a week when, after another heavy meal, he felt nauseated and dizzy with a desire to defecate. While at stool, he became faint but did not lose consciousness. The next day he consulted a local physician who told him he had a weak heart and prescribed one and one-half grains of digitalis daily, which the patient took up to the day of admission. There was no history of dyspnea, orthopnea, cough, palpitation or peripheral edema. Forty years before, a fistulo-in-ano had been excised and 26 years before, a plastic operation had been performed on his eyelids for bilateral ptosis. Otherwise his past history and family history were irrelevant.

The physical examination showed a well developed, well nourished male lying comfortably in bed, not evidently ill. A lipoma the size of an egg was present on the posterior aspect of the scalp. The pupils were equal, regular, and reacted to light and accommodation. The throat and neck were negative. The chest was emphysematous in type, the heart was not enlarged. The heart sounds were of fairly good quality

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with regular sinus rhythm, rate 60 per minute. No murmurs were heard. Blood pressure was 126 mm. Hg systolic and 90 mm. diastolic. The lung fields were clear. No organs or masses were felt in the abdomen. The reflexes were physiological.

Laboratory Studies: Examination of the urine was negative. The complete blood count was essentially normal. Wassermann and Kahn tests were negative. The blood chemistry was normal. An electrocardiogram showed slight left axis deviation. Roentgen-rays of the gastrointestinal tract revealed a rather marked antral spasm but no evidence of intrinsic gastric lesion.

Course: On the second day of his hospital stay, while straining at stool, the patient suddenly felt nauseated and then vomited. He felt weak and dizzy and was aware of a sense of fullness in his head.

The electrocardiographic effects of carotid sinus pressure with the patient in the recumbent position are illustrated in the accompanying tracings, all of which were taken in Lead II. Within one half second after pressure was applied on the right carotid sinus, complete cardiac standstill was produced for a period of 5.2 seconds. The initial beat of recovery was nodal in origin, succeeded by normal sinus mechanism (figure 1*b*). Pressure on the left carotid sinus produced almost identical results with a complete standstill of 4.4 seconds (figure 1*c*).

During the procedure, the patient complained of nausea, with a sense of fullness in the head. His face blanched and beads of perspiration covered his brow. Loss of consciousness rapidly ensued with recovery in several seconds. There were no convulsions. Slight dizziness was noted for several minutes after return of consciousness but this disappeared spontaneously. The blood pressure dropped to 80 mm. Hg systolic and 60 mm. diastolic.

The patient was then given 0.86 mg. of atropine sulfate subcutaneously and the procedure repeated five minutes later. Stimulation of the right carotid sinus produced practically no effect (figure 1*d*) whereas left carotid pressure produced sinus standstill for only 3.1 seconds after pressure for 10 seconds. The return to normal rhythm was almost immediate after compression was removed (figure 1*e*). No adverse symptoms were noted with right carotid sinus pressure and only slight dizziness with left carotid sinus pressure. There was no noticeable change in blood pressure in either case after the atropine injection.

Comment: This is a case of carotid sinus hypersensitivity in an individual with regular sinus rhythm. The induction of complete cardiac standstill by carotid sinus stimulation is the response usually obtained by virtue of specific or preponderant stimulation of the vagal terminals in the sino-auricular node. In this instance there were no essential differences in the effect of right or left carotid sinus stimulation, except that prolonged pressure on the left carotid sinus after atropinization was still slightly effective. The gastrointestinal symptoms which dominated the clinical picture may be interpreted as vagotonic abdominal effects. This viewpoint has been elaborated by Weiss et al.[2] Stern [4] has recently reported a similar case of carotid sinus hypersensitivity in which abdominal manifestations were pronounced. He believed that the disturbances of the bowel were due to severe widespread autonomic discharge involving the afferent limb of the reflex arc in the carotid sinus. It is obvious that in cases such as these in which gastrointestinal manifestations are most prominent, attention might readily be misdirected to the gastrointestinal tract in the search for the correct diagnosis.

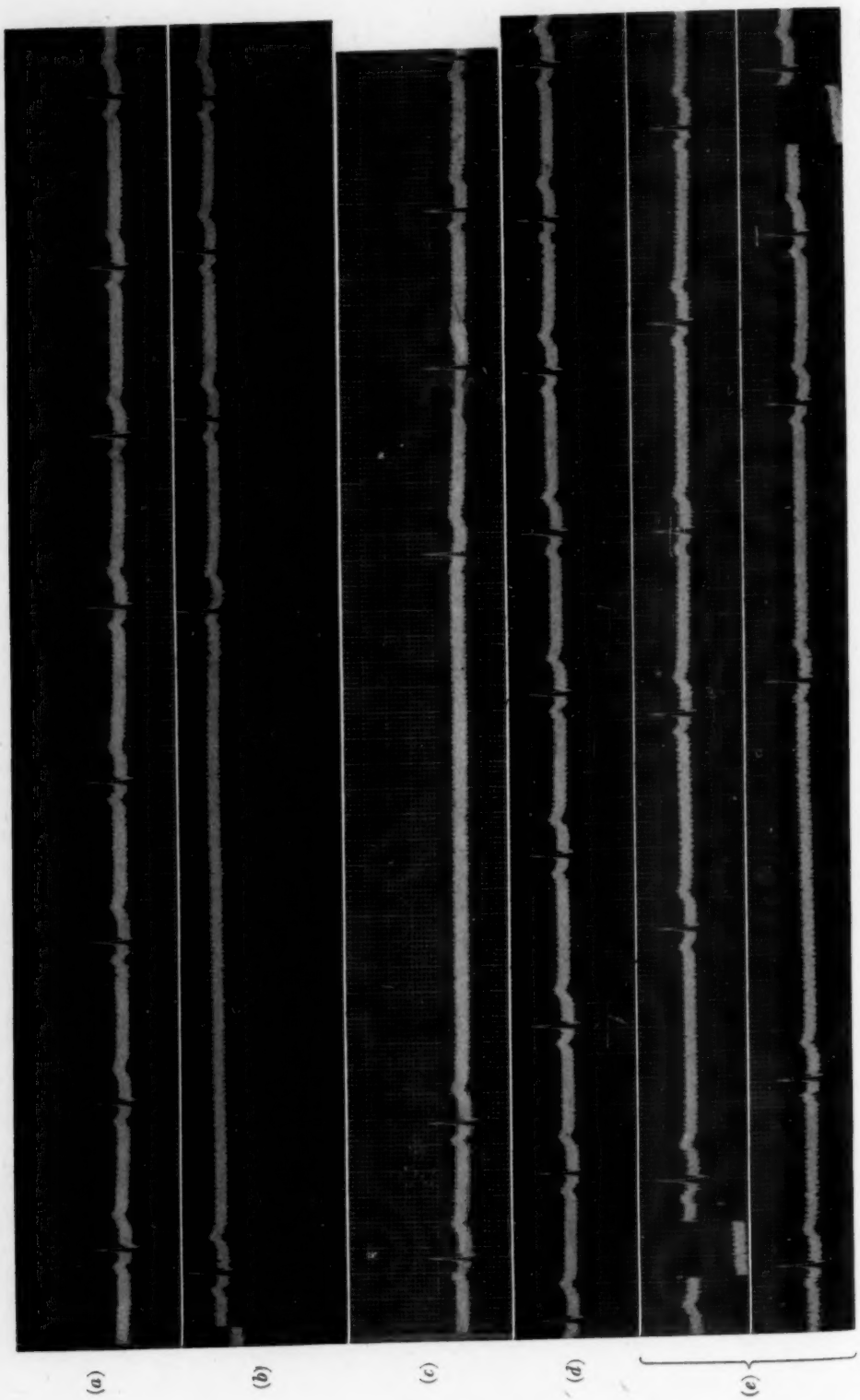

FIG. 1. (*a*) Normal electrocardiogram. (*b*) Illustrates sino-auricular standstill of 5.2 seconds following right carotid sinus pressure. The initial beat of recovery is nodal in origin. (*c*) Sino-auricular standstill of 4.4 seconds following left carotid sinus stimulation. (*d*) Illustrates no effect of right carotid sinus stimulation 5 minutes after administration of 0.86 mg. atropine sulfate. (*e*) Left carotid sinus stimulation after administration of 0.86 mg. atropine sulfate. Illustrates sino-auricular slowing up to 3.1 seconds.

Case 2. A nine-year-old girl was admitted to the New York Post-Graduate Hospital on April 1, 1940. She had been discharged from this hospital three months before, at which time she had been treated for chorea. No cardiac lesion was demonstrable then. She now complained of vague joint pains and fever which varied from 99.8° to 101° F. Physical examination showed that the heart was slightly enlarged, and murmurs indicative of mitral stenosis, mitral insufficiency and aortic insufficiency were present. The pulse rate ranged between 90 and 110. Five days after admission a heart rate of 150 was noted, suggesting the likelihood of paroxysmal tachycardia, particularly since the rate was uninfluenced by mild exertion. This was verified by the electrocardiogram (figure 2*a*). As far as could be determined, it appeared that the tachycardia had existed for about four hours.

It was decided to try carotid sinus stimulation in an effort to restore the cardiac mechanism to regular sinus rhythm. Figure 2*b* illustrates the sequence of events when pressure was applied to the carotid sinus. After one second the patient lapsed into unconsciousness and also stopped breathing. As seen in the records, ventricular asystole for 8.4 seconds was produced with evidence of auricular activity continuing during the interval at a rate of 60 to 84 per minute. Auriculo-ventricular conductivity gradually became evident. At first, this was in the form of 2 to 1 block for 5.4 seconds, followed by first grade heart block. The patient was given no stimulation and recovered consciousness shortly after ventricular contractions began. A slight headache was present for several hours after the procedure.

There were several other episodes of paroxysmal tachycardia following this, and momentary carotid sinus stimulation produced similar effects. In this case both right and left carotid sinus pressure were equally effective.

Comment: This is a case of paroxysmal tachycardia in which brief carotid sinus stimulation produced ventricular asystole, unconsciousness and respiratory standstill. Regular sinus rhythm then followed with normal auriculo-ventricular conduction after a short period of impaired auriculo-ventricular conduction. The ventricles did not manifest automatic activity at any time. There were no qualitative or quantitative differential effects as regards right or left sided stimulation.

Case 3. A 67-year-old white bookkeeper was first seen in the Out-Patient Department of the New York Post-Graduate Hospital on April 13, 1940. The presenting symptoms were attacks of dizziness and light-headedness of one year's duration. One week previous to admission, he had gone to the New York World's Fair and while looking up at the trylon he suddenly felt dizzy, fainted and was unconscious for several minutes. There were no residual symptoms following this.

For the past seven or eight months, he noticed that light-headedness and dizziness would follow any attempt to look upward. The patient had diabetes for several years, which first required insulin for control but later diet alone sufficed. He had a traumatic amputation of the third finger of the right hand when 12 years of age, herniorrhaphy at the age of 58, and the removal of a basal cell epithelioma of the right eyelid at the age of 59.

About six months prior to hospitalization, he began to complain of exertional dyspnea and occasional attacks of precordial pain with radiation down both arms. He had never noted ankle edema or cough. For five months he had been taking one and one-half grains of digitalis twice daily.

The family history was non-contributory.

The physical examination showed a well developed, moderately obese male, weighing 88 kilograms. There was marked apprehension. The mouth was edentulous

no effect of right carotid sinus stimulation. (*c*) Sino-auricular standstill of 4.4 seconds following left carotid sinus pressure. The administration of 0.86 mg. atropine sulfate. Illustrates sino-auricular slowing up to 3.1 seconds.

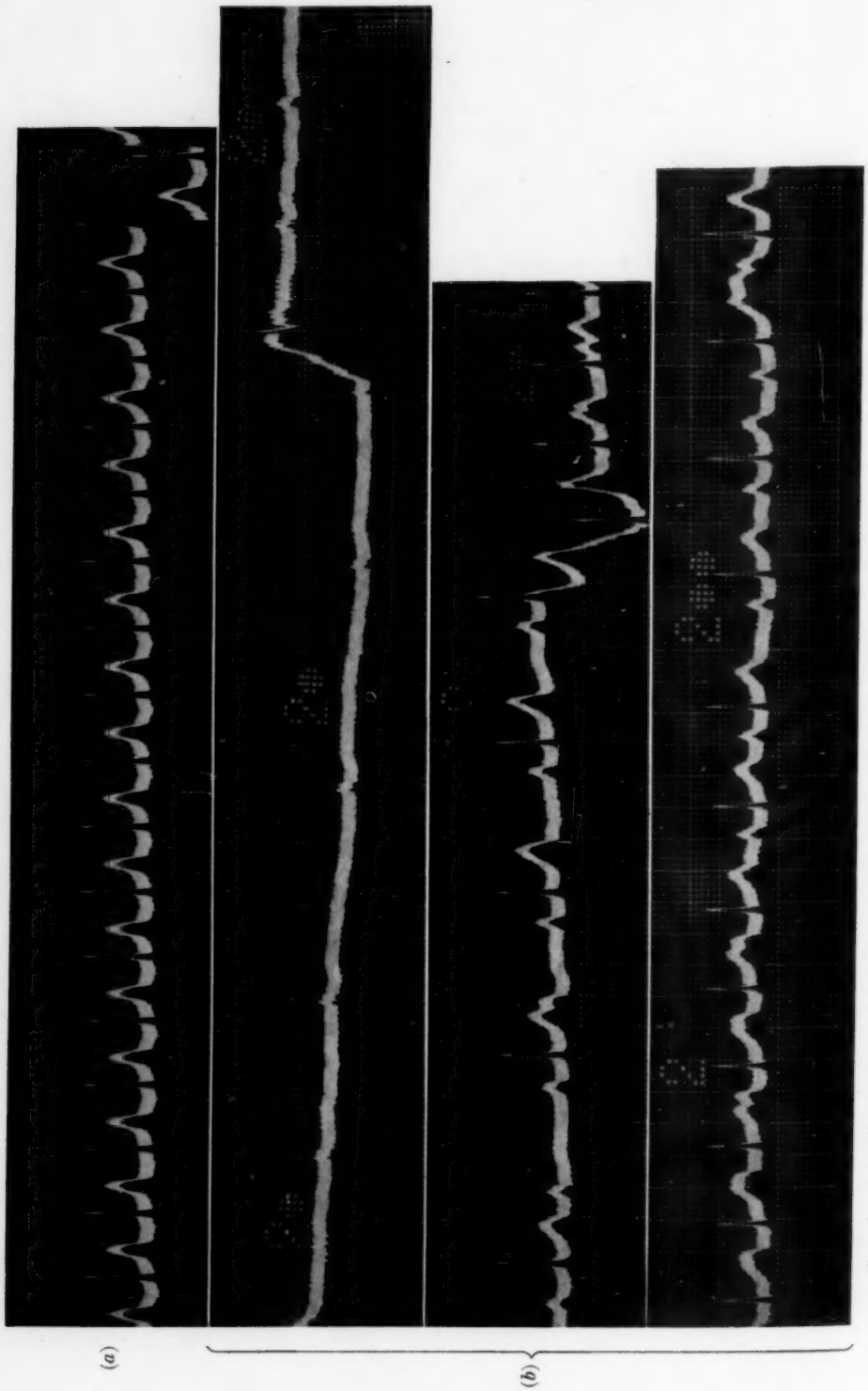

FIG. 2. (*a*) Illustrates paroxysmal auricular tachycardia with ventricular rate of 150 per minute. (*b*) Illustrates sequence of events following carotid sinus stimulation with ventricular asystole of 8.4 seconds. Auricular activity continues at rate of 60 to 84 per minute. This is followed by 2 : 1 heart block and finally by first grade heart block.

and a slight tremor of the tongue was present. The fundi showed moderate angiosclerosis. No masses were felt in the neck. The thyroid gland was normal. The chest was emphysematous in type. The apex of the heart could not be palpated; percussion revealed the left border of the heart to be 10 cm. from the midsternal line with slight widening of the area of dullness over the aortic area. The sounds were of fairly good quality and no murmurs were heard. The rate was about 68 beats per minute with a completely irregular rhythm. Blood pressure was 150 mm. Hg systolic and 84 mm. diastolic. There were transient basal râles in both lung fields. The liver was palpated at the costal margin. There was slight edema of the lower extremities. The peripheral vessels were moderately sclerotic. The reflexes were physiological.

Laboratory Studies: Urinalysis showed 1 per cent sugar and microscopic examination revealed an occasional red blood cell per high power field. The blood count was essentially normal. Wassermann and Kahn tests were negative. The blood sugar (true glucose) was 170 mg. per cent. The electrocardiogram showed auricular fibrillation (figure 3*a*).

Comment: Because of the patient's symptomatology, hyperactivity of the carotid sinus was suspected. The following studies were carried out. Pressure on the right carotid sinus for one second caused complete ventricular asystole for 6.6 seconds. The electrocardiogram showed that auricular activity was not affected and the fibrillary waves continued uninterrupted (figure 3*b*). The onset of ventricular asystole occurred immediately after pressure was applied. The offset, however, was more gradual with resumption of the original rhythm. Pressure on the left carotid sinus produced essentially the same result except for a slight increase in duration of the ventricular asystole (7.2 seconds) (figure 3*c*).

In both instances, the patient first complained of dizziness and of a feeling of fullness in the head; this was followed by loss of consciousness. Slight tonic convulsions of the upper extremities were noted which disappeared rapidly as ventricular systole returned. Hyperpnea, pallor of the face and conjugate deviation of the eyes upward and slightly to the left were also noted during the period of asystole and for a short, variable period thereafter.

The patient was then given 0.86 mg. of atropine subcutaneously and after five minutes compression of the carotid sinuses was again applied. As seen in the records, right carotid pressure elicited the same cardiac and peripheral effects as previously noted with ventricular asystole of 7.6 seconds (figure 3*d*). Left carotid pressure after atropinization, however, produced merely a transient slowing of the ventricular responses (figure 3*e*) with only slight peripheral effects, namely pallor and dizziness, but no loss of consciousness or convulsions. Apparently in this patient, the right carotid sinus was more sensitive than the left although the effects were evident in the auriculoventricular node in both instances.

Case 4. A 47-year-old Italian laborer was referred for an electrocardiogram on April 10, 1940. He had been seen by his physician about four months previously at which time he was in cardiac failure as indicated by dyspnea, orthopnea and peripheral edema. One and one-half grains of digitalis was ordered twice daily. Although he had occasionally been subject to attacks of dizziness, it was only for the preceding two months that these attacks seemed to be more frequent, and at one time he had

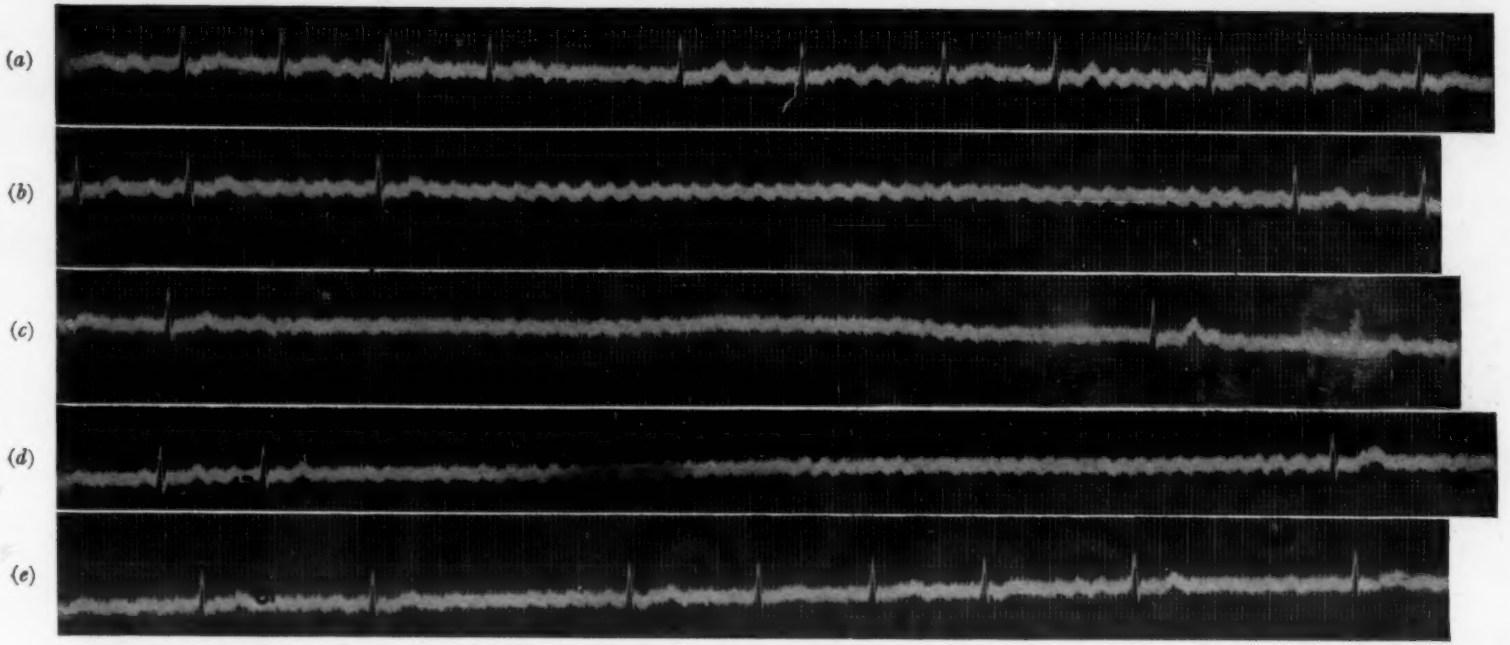

FIG. 3. (*a*) Auricular fibrillation with ventricular rate of about 65 per minute. (*b*) Illustrates ventricular asystole for 6.6 seconds following right carotid sinus pressure. (*c*) Auricular waves continued unaffected following left carotid sinus pressure. Ventricular asystole for 7.2 seconds. (*d*) Right carotid sinus pressure following administration of 0.86 mg. atropine sulfate. Ventricular asystole of 7.6 seconds. (*e*) Left carotid sinus pressure following 0.86 mg. atropine sulfate; illustrates transient slowing of ventricular response.

FIG. 4. (*a*) Illustrates auricular flutter with 2:1 heart block. Ventricular rate: 150 beats per minute. Auricular rate: 300 beats per minute. (*b*) Carotid sinus pressure in auricular flutter. Illustrates ventricular asystole for 3.5 seconds. Auricular impulses continued uninhibited.

actually fainted. The electrocardiogram showed auricular flutter with a 2:1 block, the ventricles beating at a rate of 150 beats per minute and the auricles at 300 beats per minute (figure 4*a*).

Pressure on the right carotid sinus produced effects particularly on the auriculo-ventricular node with complete ventricular asystole for 3.5 seconds (figure 4*b*). The auricular impulses continued uninhibited. The patient complained of dizziness, light-headedness and tingling of the fingers and toes. Loss of consciousness did not occur. The patient subsequently volunteered the information that the symptoms produced were almost identical with those he had noted previously, especially since taking digitalis. It was not feasible to repeat the observations on this patient following atropinization.

Comment: This is a case of auricular flutter in which momentary carotid sinus pressure promptly produced ventricular standstill. The promptness of the response and the reminiscence evoked in the patient of previous similar sensations coming on spontaneously seem to justify the case as an instance of carotid sinus sensitivity.

Discussion

The specific physiological alterations which occur in carotid sinus hypersensitivity naturally depend upon whether the cerebral, vasomotor or vagal ("cardiovascular") efferent mechanism is predominantly affected as has so clearly been elucidated by Weiss, Ferris, etc.[5, 6] We have here been concerned only with the cardiac responses. Sigler[7, 8] found that complete cardiac standstill occurred twice as frequently with right as with left carotid sinus pressure whereas high degree auriculo-ventricular block occurred more than twice as frequently with left carotid pressure as with right. Ventricular escape as well as nodal rhythm was occasionally observed. The variations in effect here depend, first, upon individual variations in sensitivity of the right and left carotid sinus, and second upon the nature of the ultimate distribution of vagus fibers to sino-auricular and to auriculo-ventricular nodes.

In general, stimulation of the right carotid sinus particularly affects the sino-auricular node and stimulation of the left carotid sinus principally affects the auriculo-ventricular node, since right vagal terminals are found in greater numbers in the sinus node and left terminals in the auriculo-ventricular nodal area. Both carotid sinuses, however, are represented in the sino-auricular and auriculo-ventricular nodes. The main effects are those of interferences with impulse formation in the sino-auricular node and its subsequent propagation along the auricles and through the conduction system.[10]

As far as the differential sinus node and auriculo-ventricular node effects are concerned, the results are completely unpredictable in man and especially so in patients with hyperactive carotid sinus.

If the sinus node is predominantly affected in any given case, sinus bradycardia or sino-auricular standstill will be produced. If the auriculo-ventricular node is predominantly affected, prolonged auriculo-ventricular

conduction of varying grades, up to complete heart block, ventricular escape, or arrhythmias originating below the auriculo-ventricular node may supervene. Premature contractions are also encountered. The ventricular portion of the conduction system is rarely influenced.

We have presented four instances of carotid sinus hypersensitivity occurring in contrasting basic rhythms, namely: regular sinus rhythm, paroxysmal auricular tachycardia, auricular fibrillation and auricular flutter.

The three cases of arrhythmia responded to carotid sinus stimulation by ventricular asystole. This was perhaps to be anticipated since the basic rhythms were autonomous as far as the sino-auricular node is concerned and were beyond its influence. The case of regular sinus rhythm responded with complete cardiac standstill, as is frequently observed in this mechanism.

The sensitizing effect of digitalis on the carotid sinus reflex has been emphasized by Weiss, Capps, Munro, Ferris, etc.[2] and is illustrated by cases 1, 3, and 4. This action probably occurs by virtue of the enhancing effect of digitalis on the vagal efferent portion of the carotid sinus reflex.

This effect should make one circumspect in the administration of digitalis to elderly individuals merely because they have ill-defined symptoms such as fatigue, weakness or dizziness, or as a routine preoperative prophylactic. The argument applies with equal validity to cardiac patients who are about to undergo operations but who are not in demonstrable failure. Case 1 was not in failure when digitalis administration was begun, and although the symptoms antedated the use of the drug, the frequency and severity of the attacks seemed definitely increased after full digitalization.

The gastrointestinal symptoms which are frequently a part of the clinical picture are also illustrated by case 1. This may be interpreted as evidence of vagotonia and the diagnostic difficulties which may ensue have already been commented upon.

The contrasting electrocardiographic effect of carotid sinus pressure in auricular flutter and in paroxysmal tachycardia is worthy of comment, particularly since it is of value in the diagnosis between auricular flutter with 1:1 response and paroxysmal tachycardia. This differentiation is often difficult even with electrocardiographic aid. In auricular flutter, carotid sinus stimulation will impair auriculo-ventricular conduction sometimes up to the point of complete block, depending on individual sensitivity, but the auricular activity will continue uninterrupted. In paroxysmal auricular tachycardia on the other hand, the rhythm, usually, will either be uninfluenced or will revert to regular sinus rhythm.

Summary

1. Four cases of carotid sinus hypersensitivity have been presented, each occurring in a different basic cardiac rhythm, namely: regular sinus rhythm, paroxysmal auricular tachycardia, auricular fibrillation and auricular flutter.

2. The results evoked following carotid sinus stimulation on each of

these cases are presented electrocardiographically. The three cases of arrhythmia responded to carotid sinus stimulation by ventricular asystole, whereas the case of regular sinus rhythm responded by complete cardiac standstill.

3. It appears impossible to predict the differential effects of right and left carotid sinus stimulation on the sino-auricular and auriculo-ventricular nodes.

4. Digitalis is shown to exert a sensitizing effect on the carotid sinus reflex, an observation that has previously been made.

5. Gastrointestinal symptoms in patients with carotid sinus hypersensitivity may present diagnostic difficulties.

6. The differential diagnosis between auricular flutter and paroxysmal tachycardia may occasionally be made by studying the electrocardiographic effects of carotid sinus stimulation.

Thanks are due to Miss Marcella Hughes for her technical assistance.

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THE IRON CONTENT OF THE SKIN IN HEMOCHROMATOSIS *

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QUANTITATIVE estimations of the iron content of skin taken from patients who have hemochromatosis have been and are exceedingly rare. Sheldon [1] in his review of world literature in 1935 was able to find only two such analyses, and the results of these were at great variance with each other. Muir and Shaw Dunn [2] found an iron content of 0.188 per cent of the dry weight of the skin, while Loeper, Ravier, and Lesure [3] reported 1.15 per cent of the dry weight as iron. In view of these discrepancies the following report is considered to be of sufficient interest and importance to justify publication.

During the past year we have made spectrographic estimations of the iron content of the skin from 15 patients, some of the specimens being obtained post mortem and some by biopsy. In many instances a clinical diagnosis of possible hemochromatosis had been made by reason of two or more of the classical symptoms and signs; namely, diabetes, pigmentation of the skin, and cirrhosis of the liver. In three instances the iron content of the skin was increased by as much as five to ten times the value we have obtained in "normal skin." That these three patients represent examples of hemochromatosis has not been proved beyond dispute, but the evidence in favor of such a diagnosis is presented in the summaries of their histories and physical findings. This paper is, therefore, presented not as a final, but as a preliminary report in the hope that others will be stimulated to make similar determinations. The incidence of hemochromatosis is such that any one group of observers may see but few examples.

Method. Specimens were obtained either by biopsy under local anesthesia or at autopsy. Biopsy specimens should weigh in excess of 200 mg. The specimen was carefully washed in distilled water to remove all blood, blotted, and then weighed. The sample was then digested in a mixture of concentrated sulfuric and nitric acid. For a biopsy specimen of 200 mg., 0.5 c.c. of concentrated sulfuric acid and 1.0 c.c. of concentrated nitric acid were used. After being taken to dryness, the ash was dissolved in 1 c.c. of the following mixture: Li_2HPO_4 2.0 gm., $Cr_2(SO_4)_3$ 20 mg., concentrated HNO_3 10 c.c., and water to 100 c.c. By means of a fine pipette three drops of this solution were then placed on each of nine crater-shaped graphite electrodes which had previously been cleaned by the method of Cholak and Story.[4] The electrodes were kept in an electric oven at 120° C. during the

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time the solution was placed on them and each drop was allowed to dry before the succeeding drop was added. The specimens were then arced in an Applied Research Laboratories spectrograph, using a 70 volt direct current with 7.5 amperes across the arc and an arc gap of 10 mm. Three exposures were taken, using three superimposed arcings for each exposure and using a step sector during the exposure. The films were read with a photoelectric densitometer measuring the densities of the chromium line at 2835 A° and the iron line at 3020 A°. Readings were also taken from the step sector divisions for the calculation of the gamma of the film. On the basis of the gamma curve the relative intensities of the iron and chromium lines were calculated and by comparing the value of this intensity with those obtained by the addition of known amounts of iron to tissue, the amount of iron in the specimen could be calculated. A blank determination was done in each case, and this value was subtracted from the value obtained for the specimen.

Results

Case	Clinical Diagnosis	Specimens Obtained at	Iron in mg./100 gm. Tissue
C. S.	Hemochromatosis	Biopsy	9.8
L. S.	"	"	9.8
H. F.	"	"	9.9
A1	Arteriosclerotic heart disease	Autopsy	1.5
A2	" " "	"	1.2
A3	" " "	"	1.3
A4	" " "	"	1.4
J	Hemochromatosis	Biopsy	5.0
S. A.	"	"	3.5
R. S.	"	"	4.4
T. G.	"	"	3.2
X. X.	Scleroderma	"	0.5
B. S.	Hemochromatosis	"	1.9
R	Lymphoma small intestine	Autopsy	2.3
H. C.	Hemochromatosis	Biopsy	0.75

The iron content of normal skin obtained at autopsy was found by Horsters[5] to be 1.05 mg./100 gm. of tissue. Our values taken from autopsy specimens agree fairly well with this value. Specimens taken by biopsy tend to run a little higher, due probably to the fact that not all of the blood could be removed. The first three values given above are greatly elevated and were obtained from patients who were considered to have a correct diagnosis of hemochromatosis. Abstracts of their histories are as follows:

Case Reports

Case 1. H. F., a white male, plumber by occupation, was seen at the Los Angeles County Hospital on numerous occasions since 1935 for the control of his diabetes. He was 56 years of age at the time of his first admission. In 1926, when he was 47 years of age, his wife first noted that his hands, forearms, face, neck, and the lower part of his legs presented an unusually deep brown appearance, as though they were

severely tanned. This pigmentation started slowly and gradually increased in the areas described. In 1934 he developed polyuria, polydipsia, and polyphagia, and experienced a concomitant weight loss of 32 pounds (150–118 pounds) during a period of five months. In 1935 because of the above symptoms and severe pruritus he was admitted to the Los Angeles County Hospital for the first time.

Of considerable interest was his past history. From the age of 15 years the patient had been a plumber and during the first 15 to 20 years of the period he had worked with copper almost exclusively, lining brewery barrels and fitting taps with copper. The tubes and pipes were made of copper, and the joints were made of lead. Also of interest is the statement that he began to drink whiskey and beer in large quantities at the age of 14 years and continued this practice until he was 39, when one of the results of his entry into the army during the war was curtailment of his drinking. At the peak of his drinking experience he was consuming about a quart and a half of whiskey and an occasional drink of beer each day. Between the ages of 39 and 56 years his consumption of alcohol was said to have been limited to two or three glasses of beer each week.

The patient stated that he had had gonorrhea at the age of 15 and "too many times since to remember." Some time between 1915 and 1925 he is supposed to have had a chancre, which was followed by a positive Wassermann reaction and a course of 20 "hip shots." What medication he received is not known, but he had no further treatment. Wassermann and Kahn tests on each admission to this hospital were negative.

At the time of his first admission in 1935 diabetes mellitus was diagnosed which was finally controlled by taking a diet of 100 gm. each of carbohydrate, fat and protein and 15 units of insulin in the morning and in the evening. At this time the pigmentation in the areas described above, and an enlarged liver palpable 5 cm. below the costal margin, with a smooth, hard and slightly tender edge, were noted. Examination of the blood at this time revealed hemoglobin 94 per cent, erythrocytes 3,350,000, color index 1.34—hyperchromic anemia. Leukocytes numbered 7,150 and in the stained smear appeared to be normal. Wassermann and Kahn tests were negative.

Between 1935 and 1939 he was admitted to the hospital on five different occasions for control of the diabetes. During these admissions the following observations were made: glucose tolerance curves (following ingestion of 50 gm. of glucose) April 30, 1935, fasting sugar 145 mg./100 c.c. blood, one hour after glucose 227 mg./100, two hours, 302 mg./100, three hours, 280 mg./100 c.c.; January 28, 1936, fasting 250 mg./100, one hour, 400 mg./100, two hours, 465 mg./100, three hours, 417 mg./100. Skin biopsy December 30, 1937 was found to contain a considerable amount of pigment in the basal cell layer of the epidermis. Sections stained for iron revealed a considerable amount of hemosiderin scattered throughout the cutis.

In September, 1939, the patient was readmitted because of extreme weakness. The additional history obtained at this time revealed that during the past five years he had been impotent and had lost his chest and pubic hair. Examination revealed a well-developed and fairly well-nourished man, 60 years of age who was most remarkable because of the pigmentation of his forearms, hands, face and neck, legs and feet. The skin over these areas was very dry, smooth, and of deep tan color, which color in reflected light took a somewhat grayer metallic appearance. No abnormal pigmentation was present over the trunk or in the mucous membranes. The chest and pubes were without hair. Blood pressure was 110 mm. Hg systolic and 78 mm. diastolic. The liver was palpable 12 cm. below the xiphoid in the midline and had a smooth, sharp, non-tender edge. There was no fluid wave, nor were there dilated abdominal veins. No other physical abnormalities were found. The following laboratory examinations were made: Urine: (voided) specific gravity 1.010. Protein 1+. Sugar and acetone, none. Microscopic examination showed 4 white blood cells

per low power field, occasional hyaline cast. Blood Count: Hemoglobin 80 per cent, erythrocytes 3,460,000, color index 1.16, leukocytes 5,250; 58 per cent neutrophiles, 37 per cent lymphocytes, 3 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles. In the stained smear the leukocytes appeared to be normal, the red cells slightly larger than normal and well filled with hemoglobin. Icterus index: 10. Blood amylase 49 mg. produced by 100 c.c. of serum (normal 70–200). Blood cholesterol 208 mg. per cent. Serum protein 5.6 per cent: albumin 3.3 and globulin 2.3. Glucose tolerance test revealed a fasting level of 192 mg. per cent, and levels of 241, 333, and 333, respectively, at one, two, and three hours after ingestion of 50 gm. of glucose.

Basal metabolic rate was minus 16 per cent. Electrocardiogram indicated left axis deviation, low voltage, and sinus arrhythmia. Hormone assay of a 48 hour urine specimen revealed no rat units of estrin (normal 0–10) and no capon units (normal 30–45) of androtin.

Microscopic examination of skin removed by biopsy revealed subepithelial iron deposits; by spectrographic estimation the iron content was found to be 9.9 mg./100 gm. of tissue.

Following discharge on October 11, 1939, the patient was well maintained on a diet of 1700 calories, containing 175 gm. of carbohydrate, 70 gm. of protein, and 80 gm. of fat, and 20 units each of regular and protamine insulin in the morning, and 20 units of regular insulin at night.

Case 2. C. S., a 52 year old white male, entered the Santa Fe Hospital on April 14, 1940, as a patient of Dr. A. M. Hoffman. He had been well until about 18 months before entry, when he first noticed that he became tired more easily than usual. This fatigue was not excessive until four months before entry. During the three months prior to entry he had noted polyuria and nocturia and for one month had noted an excessive appetite. During the four months prior to entry he had lost 10 pounds in weight (196–186). He had not noticed any abnormal pigmentation of the skin.

Past history was not significant save that in January, 1939, he had had "pneumonia of the left lung." Several urine examinations by his local physician revealed no sugar at that time.

Inventory by systems revealed no additional information.

On physical examination the patient was found to be well-developed and well-nourished and to have a marked grayish pigmentation of the hands, face, and feet. No pigmentation of the mucous membranes was noted. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. He was 5 feet 9 inches in height and weighed 186 pounds. Aside from the pigmentation mentioned above no abnormalities were noted on physical examination. The liver and spleen were not palpable, the abdominal veins were not dilated, and no indications of ascites were present.

Results of urinalysis on entry were: sp. gr. 1.032, clear, amber, acid, sugar 3+ (orange); albumin, acetone, and diacetic acid absent. Sediment was normal except for a few pus cells. Fasting blood sugar was 265 mg. per cent when he was on a diet of 150 gm. carbohydrates, 80 gm. of protein, and 100 gm. of fat. A 24 hour specimen of urine, totaling 4,000 c.c., was found to contain 1.4 per cent, or 56 grams of sugar. He continued to excrete between 50 and 110 gm. of sugar per 24 hours on the above diet, without insulin.

Results of blood count made on admission were: Hemoglobin 100 per cent (Sahli), red blood cells 5,000,000, white blood cells 3,800, polynuclear neutrophiles 38 per cent; lymphocytes 55 per cent; eosinophiles 5 per cent, monocytes 2 per cent. Blood Wassermann reaction was negative.

Skin biopsy from the thigh, April 18, 1940, was examined by Dr. E. M. Butt whose report is as follows: "The epidermis is normal in appearance. In the papillary portion of the corium a few round cells are found. Special iron stains reveal the presence of a very small amount of blue staining granular material about some of the

coiled glands. A small amount of intercellular pigment is found in the basal layers of the stratum Malpighii. This pigment, however, does not stain blue, but is of a light green color. This is in all probability iron pigment. Diagnosis hemochromatosis." Spectrographic analysis of an adjacent specimen of skin revealed 9.8 mg. of iron per 100 gm. of tissue.

Upper gastrointestinal series revealed no abnormalities.

The diabetes proved rather difficult to control because of severe reactions to regular and zinc protamine insulin. Positive skin reactions were obtained with zinc protamine insulin and regular insulin. The patient was not sensitive to crystalline insulin and was finally stabilized with no urinary sugar and a fasting blood sugar of 165 mg. per cent, on a diet of 135 gm. carbohydrate, 75 gm. protein, 100 gm. fat and 350 units of zinc crystalline insulin at 7:30 a.m. He was discharged May 11, 1940, on above management.

Case 3. H. F., a white male of 60 years, a painter by trade, entered the Los Angeles County General Hospital in September, 1939, because of amnesia of 48 hours' duration. This was apparently due to an acute alcoholic episode. When his attention was called to the peculiar color of his skin the patient recalled that it had been dark since he had been in India 40 years before, but that during the four years before entry the pigmentation of the skin of his face, neck, hands and arms had increased. He gave no other complaints aside from slight anorexia. Past and family history were not significant. On examination he was fairly well-developed and nourished and appeared to be somewhat younger than his stated age. The skin over his entire body, but especially over the exposed areas of the face, neck, hands, and arms had a blue-gray metallic hue. His blood pressure was 140 mm. Hg systolic and 100 mm. diastolic. The heart rhythm was typical of auricular fibrillation, the rate 80 per minute. The heart was slightly enlarged to percussion, but no murmurs were heard.

Auscultation and percussion revealed no abnormalities of the chest. There was no venous engorgement. The liver was palpable three cm. below the costal margin, was smooth and not tender. No other abnormalities were noted.

Roentgen-ray examination of the chest, including fluoroscopy, revealed a fibrillating heart moderately enlarged in all diameters. A few poorly defined strand-like shadows were seen in each pulmonary apex suggestive of minimal fibrotic tuberculosis without evidence of present activity. Roentgen-ray examination of the gastrointestinal tract following a barium meal revealed no abnormalities. Gastric juice contained free hydrochloric acid and there was a normal response to histamine. In electrocardiograms the T-waves in the classical leads were inverted and auricular fibrillation was indicated. Blood Wassermann and Kahn reactions were negative. Results of examination of the urine were normal. Tests for melanin were negative.

Examination of the blood revealed hemoglobin 108 per cent, 5,110,000 erythrocytes, 9,450 leukocytes, 59 per cent polynuclear neutrophiles, 27.5 per cent lymphocytes, 5.5 per cent monocytes, 6 per cent eosinophiles, and 2 per cent basophiles. Total serum protein was 6.9 per cent, serum calcium 10.4 mg. per cent, and serum sodium 318 mg. per cent. Fasting blood sugar level was 154 mg./100 c.c. Glucose tolerance test in June, 1940 revealed a fasting blood sugar of 121 mg., one hour—238, two hours—222, and three hours—141 mg. per cent. No sugar was found in the urine during the test.

Skin biopsy from the right forearm was taken for histological and spectrographic examination. The sections revealed large amounts of intradermal pigment which did not take stain typical for tissues containing an excess of iron, but gave a strongly positive test for melanin. By spectrographic examination, however, the tissue was found to contain 9.8 mg. of iron per 100 gm. of tissue.

In the interval between September, 1939, and June, 1940, the patient had developed signs of congestive heart failure and was digitalized.

Comment. We are quite certain that the first patient had hemochromatosis. The diabetes, enlarged nodular liver, and typical pigmentation together with the histological demonstration of hemosiderin in skin biopsies on two separate occasions present a rather convincing picture. The second patient, although not showing evidence of cirrhosis, did have the diabetes and the pigmentation. It is true that hemosiderin in the skin on microscopic examination does not warrant the clinical diagnosis of hemochromatosis unless the blood dyscrasias, stasis dermatitis, trauma, and Schamberg's pigmentary dystrophy are ruled out. However, none of these conditions was felt to be present in these patients.

The third patient, on the other hand, presents many problems and possibilities for speculation. It is certain at the outset that this patient does not represent a classical example of hemochromatosis. He had no diabetes; glucose was never found in his urine. On the other hand he did have an elevated fasting blood sugar and a prolonged, though not marked, rise in blood sugar during his glucose tolerance test. It is possible that this behavior of the blood sugar might be due to liver damage. In view of the later development of signs of congestive heart failure one might suggest that the enlargement of the liver was an early manifestation of right heart failure, though at no time was there evidence of increased venous pressure or peripheral edema.

The outstanding problem is the pigmentation. Because of the demonstration of melanin as the pigment one immediately must consider Addison's disease. The elevated blood pressure, elevated blood sugar and glucose tolerance curves, the normal serum sodium, and the general well-being of the patient would appear to rule this out.

Because of the high iron content of the skin, as demonstrated by spectrographic analysis, a content that was nearly identical with that found in the two patients in which the clinical evidence in favor of hemochromatosis was very convincing, we felt that a diagnosis of hemochromatosis must be considered in the third patient. The absence of hemosiderin in the stained sections of the skin certainly does not rule out hemochromatosis. Sheldon [1] reports that in 235 case reports pigmentation was absent in 38 or 16.2 per cent. Johns [7] recently published the record of a patient who was found to have hemochromatosis, proved at autopsy, whose skin contained no hemosiderin deposits.

That there should be an increase in the iron content of the skin and no demonstrable iron in this tissue by the conventional staining methods is most remarkable. This situation recalls the experience of Sheldon who found in one patient who had hemochromatosis an increase in the iron content of the brain to two and one half times the normal value without a deposit of hemosiderin as indicated by staining methods. Sheldon suggested that this might be due to an increase in the "physiological" iron not accessible to the ordinary staining methods.

Addendum

After this paper had been submitted for publication, patient 1, H. F., died, and the diagnosis of hemochromatosis was confirmed at autopsy. The iron content of the skin at autopsy was determined by the o-phenanthroline method described by Hummell and Willard (Ind. and Eng. Chem., Anal. Ed., 1938, x, 13.) A value of 7.5 mg. of iron/100 gm. of tissue was obtained. Since the iron content of biopsy specimens has been higher than autopsy specimens, this value was felt to be consistent with the 9.9 mg. value reported above in which a totally different method was used. The pituitary was found to contain large amounts of iron, 225 mg./100 gm. of tissue. This is of interest in connection with the endocrine abnormalities reported in the history.

Acknowledgment

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MENINGOCOCCAL MENINGITIS

REPORT OF FIFTY CASES, FORTY TREATED WITH SERUM AND TEN TREATED WITH SERUM AND SULFANILAMIDE*

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DURING the past decade we have witnessed important changes in the therapeutic regimen of meningococcal meningitis. The traditional method of administering serum intrathecally has been generally discontinued in favor of the intravenous route. New and improved methods of making serum have resulted in the introduction of highly concentrated antiserum and antitoxin. Supporters of serum and antitoxin using new methods of administration of these biological preparations have claimed promising results. It almost goes without saying, however, that the general fatality from this disease has remained high in spite of these innovations. It is for the purpose of critical analysis of a relatively small amount of experience with another therapeutic agent (sulfanilamide) that this report is made.

From a historical point of view many other chemicals have been used in the treatment of meningococcal meningitis. Several of them have been very popular, but during the early part of the last decade the effectiveness of immunobiological methods almost completely overshadowed all other methods of treatment. In 1936 the principle of chemotherapy was again revived by the introduction of sulfanilamide. Since then sulfanilamide and sulfapyridine have both been widely used in the treatment of meningococcal infections. Comprehensive reviews of the pharmacotherapeutic actions of these drugs have been published by many authors.[1, 2, 3, 4]

The present report is a study of 50 cases of meningococcal meningitis occurring during a four year period ending May 1939. With the exception of one case, they all were treated at the Philadelphia General Hospital. Studies of the mode of onset, symptoms and physical findings are not within the scope of this paper. These features have been thoroughly analyzed in more comprehensive monographs.

This collection of 50 cases was made up of two relatively homogeneous groups. Forty of the patients were treated with serum while the remaining 10 were treated with both serum and sulfanilamide. Age, sex, and race distributions are indicated in table 1. The most serious obstacle to this statistical analysis came about when an attempt was made to evaluate the effect of a possible change in the severity of the disease during the second half of this four year period as compared with the first half. Inasmuch as the case fatality rate for a 40 year period in Philadelphia (chart 1) has been rather

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TABLE I

Selected Clinical and Laboratory Features Occurring in 50 Cases of Meningococcal Meningitis

	Serum Treated	Serum Sulfanilamide	Total Cases
1. Sex:			
Male	28 (4)*	7	35
Female	12 (1)*	3	15
2. Race:			
White	29 (3)*	4	33
Negro	11 (2)*	6	17
3. Age groups:			
0–4	2	2	4
5–9	4 (2)*	2	6
10–19	6	4	10
20–29	11	1	12
30–39	7 (1)*		7
40–49	7 (1)*	1	8
50–59	2		2
60–69	1 (1)*		1
4. Rash:			
Petechial	12 (3)*	5	17
Purpuric	2 (1)*		2
5. Meningococci recovered from spinal fluid	37 (5)*	10	47
6. Blood cultures:			
Positive	2	2	4
Negative	13	6	19

7. Cells in spinal fluid. Average no. in 41 cases—9,243

8. Average amount of serum by route:
   - Intrathecal 58.0 c.c.
   - Intravenous 58.7 c.c.
   - Intramuscular 30.7 c.c.
   - Total average 108.8 c.c.

9. Total amount of sulfanilamide given to 6 patients = 10–25 grams.

10. Classification of cases by severity:
   - Mild 4
   - Ordinary type 12
   - Severe 29
   - Fulminating 5

11. Outcome for whole group:
   - Recovered 30
   - Died 20
   - (Autopsies 16)

* Fulminating cases.

constant, it is assumed that no unusual change in severity of the disease occurred during the time of the present study. The meningococci recovered from our patients were not typed so it is not known whether the less virulent Group II [5] was more or less prevalent during the latter half of this period. It is recognized that certain unavoidable elements of non-homogeneity were present. For example, no single physician had immediate charge of the treatment of all of the patients, thus allowing certain personal differences in methods to influence the outcome. The general scheme of treatment with serum in vogue during this four year period consisted of intraspinal, intravenous and intramuscular doses of a potent antimeningococcal serum in daily or semidaily doses. During the last two years sulfanilamide was added to the regimen.

The type and potency of the serum and its route of administration were essentially the same in both groups. Practically all of the serum used was of the highly concentrated type, 10 c.c. of which represented 30 c.c. of the unconcentrated variety. The average total amount of serum given to each patient in the serum group was 108 c.c. In the serum-plus-sulfanilamide

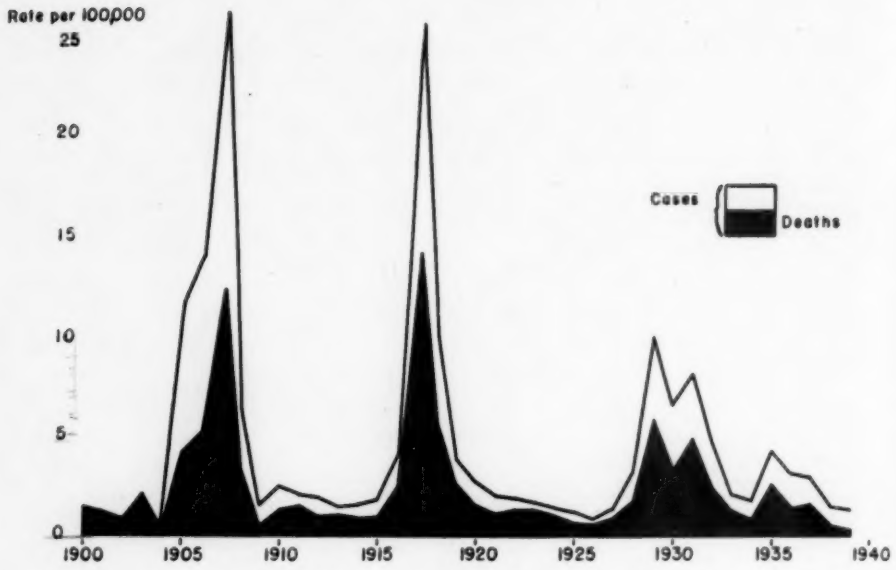

CHART I. Case rates and death rates from meningococcal meningitis in Philadelphia, 1900–1940.

group an average of 109 c.c. was given per patient. One patient was given 20,000 units of antitoxin in addition to 25 c.c. of concentrated antiserum. Sterile air was introduced into the spinal canal of a few patients. Improvement could not be directly attributed to this procedure. A summary of certain clinical and laboratory features of the 50 cases is presented in table 1.

A classification of the cases by severity, as suggested by Herrick, reveals the rather important fact that of the 50 cases, five were of the fulminating type (10 per cent) and all of these were in the serum group. Four of the fulminating cases died within 24 hours of admission. The fifth was in the hospital less than 36 hours, but treatment was delayed because the diagnosis was obscured by acute alcoholism. Compared to another group study,[6] I feel that the high fatality in the group herein reported is accounted for in some measure by the relatively larger proportion of severe and fulminating cases. Inasmuch as all of the fulminating cases occurred in the serum treated group it was considered advisable to classify them separately in order to make the two treatment groups more nearly comparable (table 2).

Table 3 lists the incidence of complications that occurred in the 50 cases. It is notable that deafness, at one time a much more common complication, occurred only once in this series. Jaundice developed in one patient following the administration of sulfanilamide; it was mild and disappeared when the drug was discontinued. The only other complication directly attributable to the sulfanilamide was vomiting, which occurred in the same patient presenting the jaundice. One of the four patients who developed bronchopneumonia died.

TABLE II

Results of Treatment of 50 Cases of Interepidemic Meningococcal Meningitis

Method of Treatment	Cases	Deaths	Fatality
1. Serum alone	35	15	42.8%
2. Serum and sulfanilamide	10	0	0
3. Fulminating cases* (4 died in less than 24 hours)	5	5	100.0%
Total	50	20	40.0%

* Fulminating cases were separated because adequate treatment was not possible before death and also because no fulminating cases occurred in the serum and sulfanilamide treated group.

The four patients presenting signs and symptoms suggestive of meningococcemia comprise the mild group. The most outstanding characteristic of the condition in these four patients was the prolonged period of illness before admission to the hospital. In these patients the condition existed 14, 21, 35, and 42 days respectively before entrance to the hospital (average 28 days). In 41 of the other patients giving a reliable history, the average duration of illness before hospitalization was 3.1 days (range one to eight days). In addition, the septicemic stage of these four patients was characterized by intermittent fever, arthralgia, rash, headache, chills and sweats. All four of

TABLE III

Incidence of Various Complications Occurring in 50 Cases of Meningococcal Meningitis

	Cases		Cases
Bronchopneumonia	4	Pyelitis (*B. coli*)	1
Meningococcemia	4	Deafness, partial	1
Otitis media	2	Myositis, lumbar muscles	1
Adenitis	2	Sinusitis	1
Jaundice	2	Alcoholism, acute	1
Interstitial keratitis	1	Chronic meningitis	1
Vomiting	1		

the patients developed meningitis [7] presumably as a result of chronic meningococcal septicemia. Three of the patients recovered promptly following the administration of small doses of antimeningococcal serum. The fourth recovered after treatment with serum and sulfanilamide.

In this era of intense interest in medical therapy there are certain features of meningococcal infections that are often overlooked. Seldom does one find reports of multiple cases occurring in families or in the same house. Few reports give the incidence of recurring attacks in the same person. It is from a careful study of these features of the disease in conjunction with specific group identification of the invading meningococcus that important epidemiologic and immunologic problems concerning meningococcal meningitis may be solved. The number of multiple cases discovered in this small

group is astonishingly high. One family of three members all developed meningitis within one month (table 4*a*). The father became ill 28 days after the onset of the same disease in his daughter and 26 days after the onset in his wife. He died after an illness of less than three days' duration. Neither the daughter nor the wife had been discharged from the hospital before the father became ill. A second group of three cases occurred in a building that housed two negro families (table 4*b*). Three children contracted the

TABLE IV

Multiple Cases in a White Family (*a*) and the Same House (*b*) Occurring in a Group of 50 Cases of Meningococcal Meningitis

	Name	Age	Sex	Race	Date of Onset	Date Adm. to Hospital	Outcome
(*a*)	1. E.W.....	12	F	W (Daughter)	3/22/36	3/26/36	Recovered
	2. L.W.....	30	F	W (Mother)	3/24/36	3/27/36	Recovered
	3. W.W....	35	M	W (Father)	4/19/36	4/21/36	Died
(*b*)	1. H.K.....	5	M	C	5/1/37	5/4/37	Died
	2. L.K.....	2	M	C	5/5/37	5/6/37	Recovered
	3. G.W....	9	F	C	5/8/37	5/9/37	Died

disease within a week. Two died, one 12 hours after admission to the hospital. In 46 families represented in this group two had three cases each (4 per cent). It should be noted that for the purposes of this study the one house in which two negro families lived is considered one family unit.

There is little uniformity of opinion regarding the incidence of second attacks of meningococcal meningitis. Stallybrass in 1931 [8] states "second attacks are almost unknown." On this basis he believes that the immunity is of "high degree." Others [9] report rare instances of second attacks. In

TABLE V

Recurring Attacks in Three Patients

Name	Age	Sex	Race	First Attack	Second Attack	Outcome
1. F.M.*.....	28	M	C	6/20/35	1/16/36	Recovered
2. J.D.*.....	28	M	W	7/28/35	11/14/35	Recovered
3. G.D.*.....	19	M	W	5/?/36	5/21/38	Recovered

* Both attacks of F.M. and J.D and the second attack of G.D. were treated at the Philadelphia General Hospital.

this group of 50 cases of meningococcal meningitis 48 persons are represented and in these 48 patients three had second attacks (table 5). Such a high incidence of second attacks would seem to indicate that the degree of immunity is not very durable.

The duration of hospitalization is of practical importance. In these two groups the average period of hospitalization for 20 serum treated patients (recovered) was 36.3 days. In the serum plus sulfanilamide treated group

the average period was 26.7 days. This is a saving of nearly 10 days per patient.

Much is being written concerning the efficacy of the various chemotherapeutic agents in the treatment of meningococcal meningitis as compared to antiserum. From a statistical standpoint the results of treatment in the two groups represented in this study may be stated as follows. Assuming there is no difference in the results of treatment by these two methods and assuming the true proportion of deaths is 15 in 35 (42.8 per cent), then the probability of obtaining no deaths in 10 cases taken at random is one in 269. Under these conditions, then, it is fair to say that there is slight probability of having 10 cases with no deaths. Since the addition of sulfanilamide is the one important difference between these two groups, I feel that it is safe to conclude that sulfanilamide produced a significant reduction in the fatality.

The studies made of the use of sulfapyridine and sulfathiazole, though meager in number, have also been very encouraging. The collected results of seven different methods of treating 2,747 cases of meningococcal meningitis are summarized in table 6. The limitations of such an accumulation of

TABLE VI

Results of Treatment of 2,747 Cases of Meningococcal Meningitis by Different Methods (Collected from the Literature August 1937 to January 1941)*

Method of Treatment	Cases	Deaths	Fatality per cent
1. Sulfadiazine (alone)	13	1	7.6
2. Sulfathiazole (alone)	70	3	4.3
3. Sulfapyridine (alone)	588	23	3.9
4. Sulfanilamide and sulfapyridine (combined)	214	17	7.9
5. Sulfanilamide (alone)	588	66	11.2
6. Serum and sulfanilamide	165	20	12.1
7. Serum (alone)	1,109	349	31.4
Total	2,747	478	

* The bibliographic references to this table will be supplied on request.

figures are threefold. The usual differences between one author and another in the management of cases of meningitis is not a serious one but is probably more important during interepidemic times. Several instances of small groups of cases (2–10 cases) were included in the table. A third and serious limitation is the fact, emphasized by Branham,[5] that during interepidemic times the less virulent Group II meningococcus predominates as the cause of meningococcal meningitis, whereas during epidemic times Group I predominates. Consequently, even though the conclusion seems valid that chemotherapy is the best method to use in treating this disease, and despite the fact that this prediction may be made for epidemic times as a result of interepidemic studies, one is by no means justified in supposing that this conclusion has been adequately proved.

Summary

1. Among 40 patients treated with serum there were 20 deaths (included among the deaths were five fulminating infections). In 10 patients treated with serum and sulfanilamide there were no deaths.

2. The incidence of certain features such as multiple cases, recurring attacks and meningococcemia, as they occurred in this group of patients, is given. Important epidemiologic and immunologic information may be obtained from a study of these features of this disease.

3. From the results of this study as well as the reports of others it seems clear that chemotherapy alone or in combination with immune serum is the most effective way of treating meningococcal meningitis.

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FATIGUE OF PATIENTS WITH CIRCULATORY INSUFFICIENCY, INVESTIGATED BY MEANS OF THE FUSION FREQUENCY OF FLICKER *

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Patients with circulatory insufficiency from heart disease and hypertension fatigue easily, not only in heavy or moderate muscular work, but also in types of light muscular work, in mental work and even in resting condition. This cannot be explained by the circulatory insufficiency alone; the increase of the oxygen consumption during those types of work is very slight, and these patients are still able to increase the cardiac minute volume more than would be necessary to cover the slightly increased demands for oxygen consumption and transportation.

This question has some practical significance. There are several million cardiac patients with slight symptoms of decompensation, who are able to perform some occupational work with slight muscular effort, and who are in fact employed at such occupations as typing, office work, shop work, secretarial work, etc., where the general fatigue is due to the fatigue of the central nervous system. It is well known that the central nervous system is especially sensitive to lack of oxygen (Heymans,[1] Simpson and Derbyshire,[2] Sugar and Gerard[3]). The literature in regard to the effects of cerebral anemia are given in the reviews of Wolff[4] and of Questal.[5] We believe that the state of the central nervous system is an essential factor in the increased fatigability of patients with heart disease or hypertension.

We (Simonson and Enzer[6]) found decrease of the fusion frequency of flicker in normal subjects after fatigue in types of work with prevailing fatigue of the central nervous system. The fusion frequency is considered to be one of the most fundamental of visual functions (Crozier[7] and Hecht[8]). The fusion frequency of flicker is that rate of successive stimuli which is just necessary to produce complete fusion and has the same effect as continuous illumination (Duke-Elder[9]). A diminution of the fusion frequency in patients would mean that the circulatory insufficiency has produced a similar or even more manifest state of fatigue than the usual occupational work in normal subjects. It would mean, at the same time, a decreased resistance of the central nervous system of patients with circulatory insufficiency against fatigue in types of work requiring only slight muscular effect. It appears to be possible to use the fusion frequency of flicker to

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judge the capacity of patients for those types of work. This is important because no other method hitherto described is suitable for this purpose. We have combined our cases of cardiac diseases and hypertension into one group, because the effect on the central nervous system is quite similar. In heart disease there is a *general* deficiency of oxygen supply; in hypertension this is due to a local vascular disturbance but often combined with a general insufficiency. The patients either were compensated or exhibited some decompensation symptoms of different degree, but none of them was bedridden.

Method

We used a rotator arrangement where the beam of light from an electric bulb (25 watt Mazda) is interrupted by a rotating disk with various openings. The light was projected onto an opal glass to obtain proper diffusion. The speed of the rotator could be easily and minutely varied by a friction screw and was measured by a mechanical revolution counter and a stop watch. The disk used had four identical openings equally spaced with a relationship of the openings (flashes) to the dark intervals of 64 : 36 (= 64 per cent). The subject was seated with his head placed on a chin rest so that the distance from the illuminated area to the eye was kept constantly at one meter. The illumination of the surroundings was kept constant with a vertical intensity of illumination at the plane of the illuminated area, facing the patient, of 2.0 foot-candles, and a vertical intensity of illumination at the subject's face, facing the machine, of 0.32 foot-candles. The illumination of the area was turned on and off by means of an electrical throw switch. The time of exposure was limited to 1.5 seconds which is the physiological optimum (Riddell [10]). The size of the illuminated area was 100 sq. mm. subtending a visual angle of one-half degree. Consequently, all of our results concerned the fovea exclusively. Binocular central fixation was used. The illumination was kept constant by means of a voltage regulator and reduced by a diaphragm to 0.0033 candle power per sq. cm.

Under these standard conditions 47 normal subjects and 22 patients with (primary or secondary) heart diseases and hypertension in different states of compensation were investigated. The vision of the 47 normals and 19 of the patients was normal or corrected to normal values with glasses. In three of the patients the vision was reduced to between 15/170 to 15/50 (cases 14, 19, and 21).

The results were checked by repeated testing. With only very few exceptions, the difference between the repeated tests was very small. The deviation of the values, when repeated during one testing, did not exceed, as a rule, 1 to 1.5 flashes. The daily variations were somewhat greater, but did not exceed, as a rule, three flashes provided that the general condition of the subject was the same. Also, in our former investigations on the effect of

fatigue in the fusion frequency of flicker,[6] we found only small daily variations. Interference by colds may greatly alter the values obtained.

Although the method is a subjective one, it has many characteristics of an objective method. The subject does not know the significance of detecting the flicker nor the actual speed of the rotator. The fact that our values coincide so closely on repeated testing, indicating an exact end point, excludes any effort on the part of the patient to influence the results. The investigation of the fusion frequency of flicker can be regarded as an excellent method for clinical investigations because it is rapid and accurate. The subject only indicates the presence or absence of flicker.

The description of our pathological cases is summarized in table 1.

TABLE I

No.	Age	Sex	Description of Patients
1	28	F	Fully compensated mitral stenosis.
2	17	F	Compensated mitral stenosis, complicated by pregnancy.
3	54	F	Hypertension 215/140. Dyspnea, headache, occasional precordial pains. E.K.G. reveals myocardial damage. Advanced arteriosclerosis of retinal vessels.
4	59	F	Hypertension 170/100. Occasional severe dyspnea, heart enlarged to left.
5	72	M	Hypertension 230/140. No symptoms of cardiovascular decompensation.
6	53	F	Hypertension 170/100. Occasional pain in chest. Moderate arteriosclerosis of retinal vessels.
7	33	F	Rheumatic heart disease. Repeated decompensation and digitalization.
8	52	M	Compensated mitral stenosis.
9	66	M	Coronary occlusion. E.K.G. Myocardial damage. Occasional precordial pain. Dyspnea on exertion. Obesity.
10	62	M	Auricular fibrillations and coronary occlusion. No cardiac enlargement.
11	73	M	Chronic glomerulonephritis and amyloidosis. Left hydrothorax. Some peripheral edema. N.P.N. 78.2 mg. per cent. Cardiac hypertrophy.
12	65	M	E.K.G. shows moderate myocardial damage, premature ventricular contractions. Peculiar sound at mitral area suggests calcification of valve. Moderate cardiac hypertrophy. Recurrent attacks of syncope.
13	65	M	Arteriosclerotic heart disease, with cardiac decompensation, peripheral edema, dyspnea, palpable liver, cardiac enlargement. Reduced kidney function. E.K.G. reveals auricular fibrillations, and myocardial damage. Blood pressure 160/100.
14	53	M	Mitral stenosis. Symptoms of decompensation (repeated unconsciousness) in history, moderate cyanosis.
15	60	M	Hypertensive heart disease; taboparesis. Blood pressure 220/130. Cardiac enlargement, dyspnea, rapid pulse.
16	41	M	Pulmonary emboli with severe pulmonary infarction 18 months previously. Occasional dizziness, dyspnea on exertion. Fatigability. No objective cardiovascular findings. E.K.G. shows low voltage and tendency to right axis deviation.
17	21	F	Hyperthyroidism and hypertension, 169/100. B.M.R.+37%. No symptoms of decompensation.
18	65	F	Pernicious anemia: 3.8 million erythrocytes; hemoglobin 78 per cent. Fatigues easily.
19	63	M	Coronary occlusion. E.K.G. confirms infarct. Angina pectoris, advanced arteriosclerosis of retinal vessels with hemorrhages.
20	30	M	Hypertension 150/120. Headaches. Fatigability. No symptoms of decompensation.
21	45	F	Essential hypertension 220/100. No symptoms of decompensation.
22	24	F	Hypertension and cardiac decompensation due to chronic glomerulonephritis.

Results

We found a clear cut influence of age on the fusion frequency [13]; this began definitely after the age of 30; the values of older subjects did not exceed a fusion frequency of 45 flashes per second, but younger subjects may show as low values as those of older people. The lowest normal value of 47 normal subjects was 40.2 flashes per second; the mean value for all age groups was 44.9.

We do not know the actual values of the fusion frequency of our patients before the development of their disease state. Thus, we are not able to ascertain the correct decrease of the fusion frequency. We can conclude only that there is a pathological decrease, if the value is lower than the lowest normal value obtained in a sufficiently large number of controls. But this does not exclude a pathological decrease in any case in which the values are somewhat higher than the lowest values.

Only two values were found to lie between the normal average (A) and the lowest normal limit (L) (table 2). One was observed in a patient with

Table II

Fusion Frequency of Flicker in Patients with Circulatory Insufficiency

Case No.	Flashes per sec.
	A = Normal Average = 44.9
1	44.0
2	41.6
	L = Lowest Normal Limit = 40.2
3	31.4
4	35.6
5	37.8
6	36.0
7	34.0
8	37.0
9	35.0
10	32.5
11	39.0
12	40.0
13	34.8
14	32.6
15	37.6
16	39.1
17	38.8
18	33.0
19	30.8
20	36.0
21	36.0
22	34.8

fully compensated mitral stenosis, who felt very well on the day of investigation and during the following four months that she was observed. The other, also, was found in a patient with compensated mitral stenosis, complicated, however, by four months' pregnancy at the time of first examination. As this patient was very young, it is quite possible that the findings indicated a considerable decrease of fusion frequency. A second examination of this

patient was performed three months after the first examination. The values were identical within the experimental error: first examination, 41.6; second examination, 41.2.

All other 20 values are below the lowest normal limit, i.e., they must be regarded as pathologically decreased. The mean value of the groups with circulatory diseases is remarkably lower than that of the normal group. The mean value of all normal subjects is 44.9, that of all 22 patients is 36.1 in which the high values of two perfectly compensated patients are included, although these cases may be regarded as normal with respect to subjective symptoms, actual working capacity, and clinical data. The flicker at a speed of 36.2 flashes per second is easily manifest to the normal subjects. Thus, in all clinical cases the fusion frequency is markedly decreased. This must be attributed to an oxygen lack in the visual pathway as a whole resulting from the circulatory insufficiency.

No parallelism was found between the height of the blood pressure and the decrease in the fusion frequency in the cases with an uncomplicated hypertension but with normal vision.

We found that cases of hypertension, when complicated by general circulatory decompensation (cases 4, 13 and 22), show distinctly lower values of fusion frequency than cases of hypertension without clinical circulatory disturbances (cases 5, 15, 17 and 20). Three cases of hypertension showed advanced arteriosclerotic changes of the retinal vessels (cases 3, 6 and 19). No decompensation was present in case 6, but in cases 3 and 19 there were some symptoms of decompensation. The fusion values were all lower than could be explained by the hypertension alone or the findings of some decompensation symptoms. We feel that the presence of advanced retinal arteriosclerosis indicates a more severe local vascular involvement of visual pathways as a whole and explains the comparatively lower values.

Riddell [10] believes that a lowered visual acuity in otherwise normal subjects decreases the fusion frequency. We found, however, in some preliminary experiments that this finding cannot be generalized because some forms of lowered vision are not accompanied by decrease of the fusion frequency. This is to be a subject for a later communication.

Consequently, we believe that the factors mentioned above are more significant in reducing the fusion frequency than the lowered visual acuity found in cases 14, 19 and 21.

Cases 11, 12 and 16 with no hypertension, but with some cardiac involvement, and some slight symptoms of cardiac decompensation, showed only a slight decrease in the fusion frequency. When more cardiac involvement is present, as in cases 7, 14 and 22, without hypertension, the fusion frequency is significantly lower.

The analysis of the material shows that there is undoubtedly a relationship between the value of the fusion frequency and the actual state of the patient. The worse the condition of a patient, the lower was the value of fusion frequency.

The method will give even better results when used repeatedly on the same patient. In patient 10 we found a fusion frequency of 32.5 in our first investigation. With the improvement in his general condition, after an interval of eight weeks, the fusion frequency was likewise increased to 35.6, but still pathologically decreased. The following experiment is a further illustration of the importance of the general status for the fusion frequency. Shortly after obtaining a fusion frequency of 37.6 on patient 15, he was subjected to the mild exertion of the finger ergograph. During this performance he suffered a slight collapse without unconsciousness. After 15 minutes of recovery the fusion frequency obtained was 35.2 and on rechecking the same value was obtained. This reduction is quite significant since it exceeds the experimental error by 100 per cent.

Discussion

In local or general circulatory insufficiency there is an anoxemia of the tissues including the brain (Altschule,[11] Wiggers [12]). Our data are further strong evidence of the importance of an adequate oxygen supply for the proper function of the visual pathway.

If this view is correct other pathological types of insufficient oxygen supply should show a decrease of the fusion frequency. We investigated a patient (No. 18) with pernicious anemia and found a fusion frequency of 33.0. In this case the lack of oxygen supply is not due to mechanical insufficiency of the circulatory system but to the diminished oxygen content of the arterial blood. The effect, however, in regard to the fusion frequency is the same. This experiment indicates that it is the lack of oxygen to the central nervous system and retina which is responsible for decreasing the fusion frequency in heart diseases and hypertension.

Thus, the decrease of the fusion frequency in circulatory insufficiency shows the deterioration of an important sensory function, which to a certain degree is an indication of the state of the whole nervous system. Our results may also be regarded as suggesting the physiological background for the increased fatigue in types of work with prevailing fatigue of the central nervous system and with only slight muscular effort. The fusion frequency of patients with *slight* decompensation symptoms during rest is as low as in some normal subjects in the state of pronounced fatigue, and in patients with *moderate* symptoms of decompensation (such as dyspnea on exertion, some edema in the evening, some cardiac enlargement, etc.) it is even lower.

Summary

1. The fusion frequency of flicker has been investigated in 22 patients with hypertension and heart disease.

2. With the exception of two fully compensated cases of mitral stenosis, all values of the patients are lower than the lowest normal values observed in 47 normal subjects.

3. The decrease of fusion frequency throws additional light on the actual state of the patient.

4. The decrease of fusion frequency is directly concerned with the oxygen supply to the visual pathway as a whole.

5. The decrease of the fusion frequency indicates a certain permanent degree of fatigue of the central nervous system and explains also the decreased working capacity of patients with circulatory impairment in types of work with slight or no muscular effort.

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SULFONAMIDES: PASSAGE INTO SPINAL FLUID AND RECTAL ABSORPTION *

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The increasing importance of sulfathiazole in the treatment of bacterial infections makes it desirable to elucidate any differences from the more familiar sulfanilamide, particularly concerning distribution in the body. Thus it has been thought that sulfathiazole penetrated into the spinal fluid less readily than sulfanilamide, and was also less readily absorbed from the rectum. This report presents results on these aspects of the sulfonamides in animals and patients.

Spinal Fluid Penetration

Sadusk and coauthors,[1] in 1940, claimed that spinal fluid concentrations of sulfathiazole, from 0 to 25 per cent of the simultaneous blood values, occurred after four hours of administration of the drug, and from 10 to 20 per cent of the blood levels after 24 hours. Carey [2] reported similar low concentrations as compared with the much higher penetration previously reported by Marshall and coworkers for sulfanilamide.[3] We have compared the blood and spinal fluid levels of sulfanilamide, sulfapyridine, and sulfathiazole in dogs and patients.

Dogs. Two unanesthetized dogs were given the drugs either orally or rectally, the usual dose being 0.15 gm. per kilo body weight. Simultaneous blood and spinal fluid estimations of the drug were made at intervals from four to 24 hours after administration. No local anesthetic was used for the spinal punctures. Nine comparisons with sulfanilamide were made: the blood concentrations varied from 1.1 mg. (free) to 14.6 mg. per cent (free), with an average spinal fluid concentration of 81 per cent (range, 50 to 100 per cent). The time within the limits of four to 24 hours after drug administration appeared to have no effect on the relative concentrations. Five comparisons with sulfapyridine showed less regularity: spinal fluid concentrations varied from 0 to 100 per cent of the blood level, with blood levels from 0.1 to 5.2 mg. per cent. Five comparisons with sulfathiazole showed consistently low spinal fluid concentrations: the spinal fluid level was from 0 to 29 per cent (average 14 per cent) of the blood concentration, except in one trial in which the 24 hour level of spinal fluid sulfathiazole was 250 per cent of the blood level. Thus it would appear that penetration

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of sulfathiazole into the spinal fluid is much less than that of sulfanilamide, in dogs. However, a paradoxically high level may be obtained in the spinal fluid, when the blood is nearly cleared of the drug and before it has all escaped from the spinal canal.

Patients. Ten comparisons of blood and spinal fluid concentration of sulfathiazole were made in patients without meningitis. With blood concentrations (free) varying from 0.3 mg. to 8.3 mg. per cent, the spinal fluid concentrations varied from 0 to 44 per cent of the blood level, and averaged 20 per cent.

Meningitis. For comparison with these values for patients without meningitis, some observations were made on patients with meningeal infections.* The results are summarized in table 1.

It is seen that spinal fluid penetration of all three of the sulfonamide drugs used was considerable. In contrast to the 20 per cent penetration of sulfathiazole through normal meninges, the average in patients with meningitis was 53 per cent. This was somewhat less than the 82 per cent average for sulfanilamide, and the 89 per cent average for sulfapyridine. However, these percentages must be regarded as indicative of general trends due to the relatively few determinations which could be made. There was no consistent change in spinal fluid penetration of drug as the meningitis subsided in patient 5, or increased in severity in patient 6, in whom it ended fatally.

Rectal Absorption

Several reporters have claimed that sulfathiazole is poorly absorbed from the rectum, although no satisfactory comparisons of rectal and oral absorption of the different sulfonamide compounds have been made previously. Reinhold and coworkers,[4] in 1939, were among the first to mention the poor absorption of sulfathiazole. Both Hartmann and coworkers [5] and Neal and coworkers [6] have administered sulfapyridine or sodium sulfapyridine by rectum. In one trial, in which the sodium salt was given in 2 per cent solution, the former authors [5] reported a blood concentration of 4 mg. per cent. Local irritation was not mentioned. A more complete study of the absorption of sulfanilamide has been reported by Marino and coworkers,[7] and particularly Turell.[8] Marino and coworkers reported that sulfanilamide was absorbed somewhat from suppositories, though more definitely from a 1 per cent solution. Turell claimed that both solution and suppositories were effectively absorbed, repeated dosage resulting in blood concentrations as high as 9 to 11 mg. per cent (total). Turell also reported that sulfanilamide was absorbed from an isolated rectal loop in man. We have made further studies in dogs and in patients.

Dogs. We administered sulfanilamide, sulfapyridine and sulfathiazole, in turn, to two dogs, both by mouth and by rectum, in doses of 0.15 gm. per

* We are grateful to Dr. H. K. Faber, Professor of Pediatrics, Stanford University School of Medicine, for permission to include patients 4, 5, and 6.

TABLE I

Comparative Blood and Spinal Fluid Concentrations of Sulfonamides in Meningitis †

Day	Drug	Drug Concentration		
		Blood, mg. per cent	Spinal Fluid, mg. per cent	Per Cent Penetration into Spinal Fluid
	Patient 1. Pyogenic meningitis			
1	Sulfanilamide started			
7	" "	4.5	4.2	93
7	Sulfapyridine started			
9	" "	6.1	4.4	72
10	Sulfathiazole started			
14	" "	1.7	1.2	71
16	" "	2.7	1.3	47
	Patient 2. Pneumococcus meningitis			
1	Sulfapyridine started			
16	" "	6.2	3.7	60
	Patient 3. Influenzal meningitis *			
Single dose	Sulfathiazole	2.5	1.6	
	Patient 4. Lymphocytic choriomeningitis			
Single dose	Sulfanilamide	8.0	7.6	95
	Patient 5. Influenzal meningitis			
1	Sulfanilamide started			
2	" "	14.5	8.5	59
3	" "	8.6	7.2	83
3	Sulfathiazole started			
4	" "	6.8	3.2	47
5	" "	9.1	3.8	42
6	" "	9.3	2.2	23
7	" "	7.3	3.2	44
8	" "	5.5	3.6	65
	Patient 6. Influenzal meningitis			
1	Sodium sulfathiazole started			
2	" " "	8.4	4.1	49
3	" " "	6.0	3.0	50
4	" " "	5.3	3.2	60
7	" " "	3.6	3.1	86
8	Sulfanilamide started			
10	" "	3.6	2.8	78
10	Sodium sulfapyridine started			
13	" " "	14.4	7.7	53
14	" " "	13.2	8.6	65
15	" " "	7.8	9.5	122
16	" " "	6.0	4.2	70
16	" " "	14.0	11.5	82
17	" " "	8.4	12.6	150
18	" " "	6.2	5.5	89
19	" " "	5.2	6.5	125

* Spinal fluid estimation was made a few hours later than the blood estimation; dosage constant.

† Days in first column of table mean total consecutive days of medication, except where single doses are indicated, and blood and spinal fluid estimations were made on particular days indicated.

kilo body weight. A total of 16 administrations was given. Blood samples, obtained two, four, six, and 24 hours after administration, were analyzed for the drug concentration. Figure 1 illustrates the results obtained in dog 1, the results with dog 2 showing roughly the same relationships. It is seen that, although all three drugs were quite well absorbed by mouth, only sulfanilamide was absorbed appreciably from the rectum.

In these two dogs, the drug was given by rectum as a powder in an open half of a gelatin capsule, and followed by 10 to 20 c.c. of water through a rubber catheter. Since it was assumed that the drug did not ascend farther than the rectum, or lower colon, dog 3 (5 kg.) was used to compare rectal absorption with absorption higher in the colon, where large rectal infusions

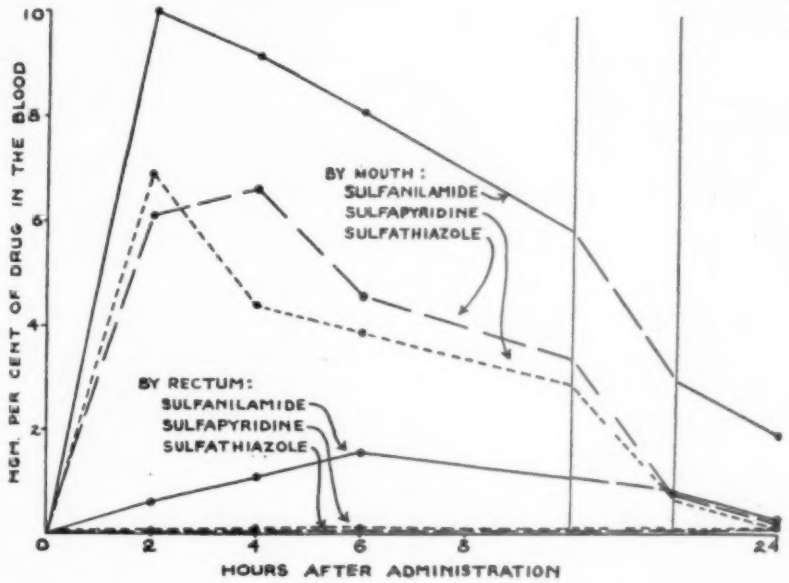

FIG. 1. Comparative absorption of sulfonamides by mouth and by rectum in dog 1.

of the drug in solution might at times be expected to reach. Under sodium pentobarbital anesthesia, the rectum was ligated near the anus, and a ligature was applied at the splenic flexure of the colon. Into the segment thus formed, 0.5 gm. of sulfanilamide, in 1 per cent solution, was introduced. Blood samples were taken every 20 minutes, and at the end of one hour, the blood concentration of sulfanilamide being 4.4 mg. per cent. The contents of this segment were then removed by thorough washing with normal physiologic salt solution. After an interval of two hours, the blood concentration had fallen to 3.4 mg. per cent. At this time, a new segment reaching from the splenic flexure of the colon to four inches past the ileocecal valve was tied off. Into this loop, 0.25 gm. of sulfanilamide in 1 per cent solution

was introduced (half the former dose), and blood samples again taken at 30 minute intervals. At the end of one hour, the blood sulfanilamide concentration was 11.3 mg. per cent. Accordingly, the absorption from the upper colon was found to be far superior to that from the rectum, half the dose of sulfanilamide giving twice the absorption, as indicated by the blood concentration of the drug.

Patients. Observations somewhat similar to those in dogs were made in 16 patients in order to compare rectal absorption of sulfanilamide, sulfapyridine and sulfathiazole. The compounds were administered in 4 gm. doses, suspended in 30 to 50 c.c. of water, being given easily from a triumph glass syringe through a larger rubber catheter. Blood was obtained two, four, six, and 24 hours after administration for determination of the drug content. All values reported are for the free forms of the drugs, and are summarized in table 2.

TABLE II

Rectal Absorption of Sulfonamides in Patients

Patient	Body Weight, kg.	Dose, gm.	Blood Concentration (mg. per cent)			
			2 hours	4 hours	6 hours	24 hours
Sulfanilamide						
Be	45	4	1.8	2.7	2.7	1.3
V.E.	75	4	1.8	2.4	2.6	1.7
Sa	81	4	1.8	2.2	2.5	1.4
Ge	69	4	2.3	3.4	3.6	2.0
Ga	82	4	2.6	2.6	2.4	0.7
Sa	81	10	0.6	2.0	2.0	1.0
Ga	65	10	2.8	—	—	0.9
Ya	57	10	2.9	2.7	2.4	0.9
Ph	58	10	3.0	—	—	1.5
Ra	68	10	3.1	—	—	3.5
Ca	58	10	5.0	6.5	6.7	2.2
Sl	58	10	9.4	8.7	11.9	10.8
Sulfapyridine						
Na	74	4	0.1	—	0.1	0
Sm	67	4	0.2	—	0.2	0
Ga	82	4	0.2	0.2	0.3	0.1
Sa	81	4	0.3	0.2	0.2	0
Mo*	64	4	0.6	0.5	0.4	—
Sulfathiazole						
Re	60	4	0	0	0	0
Pa	55	4	0	0	trace	0

* Sodium sulfapyridine.

It is clear that sulfapyridine and sulfathiazole were not substantially absorbed from the rectum. In a single trial with a solution of sodium sulfapyridine this was found to be too irritating to be retained more than one-half hour. Sulfanilamide, however, was readily absorbed, the average blood level at six hours, after 4 gm. doses, being 2.8 mg. per cent, and at 24 hours,

1.4 mg. per cent. The rather uniform blood levels reached with 4 gm. doses, despite a considerable variation in the weight of the patients, raised a question as to whether the drug was absorbed until a constant blood level was reached, depending on a fixed diffusion gradient from a saturated solution of sulfanilamide. That this was not entirely true was shown by the results following the administration of 10 gm. doses. Here, although in certain patients the blood level did not rise higher than with 4 gm. doses, in others it rose to rather high levels. According to these results, rectal absorption of sulfanilamide was found to be variable, but in no case did it fail to be absorbed. Even with the smaller doses in large patients, a blood concentration of over 2 mg. per cent was present six hours after rectal administration of the drug.

As a further observation on the constancy of rectal absorption, 0.5 gm. of sulfanilamide, with 10 c.c. of water, was placed in a dog's rectum (5 kg.), and the anus was closed by suture. It was found that the blood concentration of sulfanilamide rose steadily, until at eight hours it had reached a peak of 4.9 mg. per cent, after which it fell gradually until at 27 hours it was 1.9 mg. per cent. There was no evidence of a long plateau which could be interpreted as a period when a fixed diffusion gradient was maintaining a constant blood level from a saturated solution in the rectum. This confirmed the observations in patients.

Discussion

That sulfathiazole penetrates into the spinal fluid poorly in normal dogs, and even in patients with meningeal inflammation only about half as well as sulfanilamide, should not be interpreted as indicating that this drug has no place in the treatment of meningitis. If the infecting organisms are decidedly more susceptible to sulfathiazole than to sulfanilamide, as is apparently the case with the staphylococcus, sulfathiazole should be used. In pneumococcus infections, sulfapyridine has about the same effectiveness as sulfathiazole. The former drug, therefore, would appear to be superior in pneumococcus meninigitis, owing to its better penetration, unless the greater toxicity of sulfapyridine is a consideration. Occasionally, spinal fluid concentrations were found by us which were higher than the simultaneous blood levels of sulfapyridine and sulfathiazole. This may indicate merely a slow disappearance of these drugs from the spinal fluid, as compared to a more rapid escape from the blood.

The results on rectal absorption indicate that only sulfanilamide has a possible therapeutic value by this route. The rather low blood levels obtained, after single doses, may be increased with repeated administration of large doses, but the rectal route remains a relatively inefficient method of administration. However, this does not mean that it is useless. When vomiting interferes with oral administration, and vigorous therapy is not necessary, the ease with which a nurse can give sulfanilamide by rectum may make it the route of choice. Similarly, postoperatively, if drugs are contra-

indicated by mouth, or in children who resist oral medication, rectal administration might occasionally be useful. Prophylactically, in operations on the rectum, it might also be valuable. The administration of a suspension of the drug has the advantage of simplicity, although greater absorption is to be expected from large volumes of solution, which ascend higher up the colon. Since sulfanilamide settles quickly from suspension the mixture should be vigorously stirred, immediately sucked up into a large syringe and injected at once through a catheter previously inserted into the rectum. The syringe is then removed, partly filled with water, and the drug remaining in the catheter is washed into the rectum.

Although other reporters have described the administration of sulfapyridine rectally, it would appear that repeated, large doses in large volumes of water would be necessary to obtain satisfactory blood concentrations of the drug. Sodium sulfapyridine, however, has been claimed to be satisfactory, although in our single observation, it was too irritating to be retained. If given in a large volume of water, it might have the disadvantage of acting as an enema, unless given very slowly.

Why slight differences in molecular size and constitution so abruptly change the penetrating powers of the sulfonamides through biological membranes is not understood. The superior penetration of sulfanilamide through the meninges and the rectal mucosa is in agreement, however, with its more ready absorption from the upper alimentary tract. Fundamental studies of these interesting differences between the sulfonamides are desirable.

Conclusions

1. Sulfathiazole, when given by mouth, was found to enter normal spinal fluid to a concentration of only about 20 per cent of the simultaneous blood concentration; roughly twice this concentration would penetrate through inflamed meninges.

2. Sulfapyridine and sulfanilamide penetrated more efficiently into the spinal fluid in meningitis, the concentrations in the spinal fluid approaching the blood levels of these drugs.

3. Rectal absorption of sulfapyridine and sulfathiazole was practically nil in dogs and patients.

4. Rectal absorption of sulfanilamide, although variable, was always considerable, and, when low blood concentrations will suffice, rectal administration may be a valuable method for therapeutic administration of this drug.

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STREPTOCOCCAL MENINGITIS

FOUR CASES TREATED WITH SULFONAMIDES IN WHICH THE ETIOLOGICAL AGENT WAS AN UNUSUAL STREPTOCOCCUS*

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The meninges, like the synovial membranes and the endocardium, are unique in that they are frequently the site of infections caused by organisms not ordinarily regarded as highly pathogenic for man.

It is, therefore, to be expected that many varieties of streptococci should have been observed to be etiological agents in meningitis. It is apparent that this is so from a survey of reported cases of this disease. From such a study it is difficult to assess the relative frequency of the various types of streptococci in meningitis or to form an accurate estimate of mortality rates for types other than the hemolytic. The Lancefield technic [1] has not been applied in many instances of streptococcal meningitis so that the distribution of Lancefield groups as etiological agents in streptococcal meningitis has not been established.

It is the purpose of this paper to summarize the available information in regard to streptococcal meningitis, particularly in reference to its etiology, mortality under non-specific therapy, and in relationship to the sulfonamide drugs, and to present four cases, all of which received chemotherapy, of streptococcal disease of the meninges caused by unusual streptococci.

Incidence and Predisposing Factors

Streptococci are responsible for approximately 17 per cent of 1566 cases of bacterial meningitis described by Neal.[2] No evidence as to the frequency of hemolytic and non-hemolytic varieties has been presented. In this clinic during the last seven years 36 cases of bacterial meningitis have been observed. Six, or 16 per cent, of these were caused by streptococci, of which five were hemolytic and one non-hemolytic.

Lancefield grouping of hemolytic streptococci derived from cases of meningitis has been applied in only a few instances. The vast majority of such strains have been shown [3, 4] to be members of Group A. Hare [4] mentions three instances of infections due to Group B, but details are entirely lacking. Thomas [5] has described a case in which "minute" hemolytic streptococci were the etiological agents. These may have been members of Group F.[6] Biological and serological studies have rarely been applied to strains of non-hemolytic streptococci obtained from the meninges.

Thirty-eight per cent of all cases of streptococcal meningitis [7] are asso-

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ciated with otitis media; 24 per cent follow injuries to or operations upon the skull and spine; 10 per cent follow upper respiratory infections; 5 per cent occur in association with sepsis; 19 per cent are of unknown etiology; and the remainder are associated with a variety of conditions. The hemolytic streptococcus was presumably responsible for most of these infections. Eighteen cases of non-hemolytic streptococcal meningitis have been described [8, 9, 10] in which it is possible to determine the predisposing factors involved; 22 per cent were associated with otitis media; 44 per cent followed operation or injury; 11 per cent followed upper respiratory infections; and there were 11 per cent in which no evidence of previous disease was obtainable. Trauma to the central nervous system is, therefore, nearly twice as frequently present in these cases as in hemolytic streptococcal disease of the meninges.

Mortality and Response to Therapy

Neal,[2] from her very large experience, stated in 1938 that the mortality rate of hemolytic streptococcus meningitis was 95 per cent before the introduction of the sulfonamide drugs. Nearly all of these cases were probably caused by streptococci members of the Lancefield Group A. That certain of the recovered cases may not have been, is emphasized by the case of Rosenberg and Nottley [8] in which the streptococcus isolated from the spinal fluid was described as "partial hemolyticus" and was probably a member of some other group.

With the application of sulfonamide therapy approximately 20 per cent of individuals suffering from hemolytic streptococcal meningitis have died.[11]

It is very much more difficult to obtain accurate data as to the mortality rate of non-hemolytic streptococcal meningitis. Fifty-nine cases of spontaneous recovery from streptococcal meningitis have been reported[8, 9, 10] in which the etiological organism has been described in relation to its action upon blood agar. Twenty-seven per cent of these were non-hemolytic or formed green pigment. Since 17 per cent of cases of streptococcal meningitis in this clinic were caused by this type of organism it seems fair to conclude that the mortality rates of meningitis due to hemolytic and non-hemolytic streptococci are approximately the same. Five cases of meningitis due to non-hemolytic streptococci or *Streptococcus viridans* have been described [10, 12, 13] in which sulfonamides have been used. Four recovered and one died.

Four additional cases in which streptococci other than members of the Lancefield Group A were etiological agents in infections of the meninges will now be described. All received chemotherapy; three recovered and one died. The bacteriology of each is presented, the organisms being classified by the system proposed by Sherman [14] and by the Lancefield technic using precipitating antigens prepared by a modification of the formamide method of Fuller [15] and the micro method of Brown.[16]

Case Reports

Case 1—Lancefield Group B Meningitis. Mrs. A. C., a 48-year-old white housewife, entered the hospital January 4, 1941 demonstrating the signs of compression of the spinal cord at the level of the twelfth thoracic vertebra without evidence of other disease. Examination of the blood and urine was not remarkable. Laminectomy was performed on that day and a meningioma was removed. The post-operative course was associated with fever for two days followed by two days of normal temperature. At this time there was a chill, rapid rise in temperature to 39° C., accompanied by the development of headache, stiffness of the neck and malaise. On the following day cisternal puncture was performed and a cloudy spinal fluid obtained which contained 4,000 cells per cubic millimeter all of which were polymorphonuclear. The sugar content was 100 mg. per 100 cubic centimeters. Culture of the fluid and of the blood revealed hemolytic streptococci. On the following day sulfapyridine therapy was instituted, 14 grams being administered by mouth over a period of 48 hours. The temperature gradually returned to normal and she made an uneventful recovery, except for the development of a severe facial and oral herpes simplex on the third day after the onset of the meningitis. It should be pointed out, however, that the blood culture was already sterile before the onset of drug therapy, that the temperature was markedly lower, the neck less stiff, and that she was obviously improving.

Bacteriology. Hemolytic streptococci were recovered from both the blood and the spinal fluid. In the former instance there was one colony, and in the latter 10 per cubic centimeter. These organisms have been demonstrated by the precipitin reaction to be members of the Lancefield Group B.

Comment. This is a case of meningitis following laminectomy in which the etiological agent was a hemolytic streptococcus of the Lancefield Group B. The infection was characterized by a sharp onset with positive blood and spinal fluid cultures and the typical signs of meningitis. The spinal fluid sugar content was normal. Very marked improvement occurred before sulfonamide therapy was begun and the blood culture had become sterile. It is, therefore, unlikely that chemotherapy exercised an especially beneficial effect on the course of events in this case.

Case 2—Enterococcus Meningitis. Mr. R. M., an 18-year-old white male school boy, entered the hospital October 9, 1940 with a complaint of mastoiditis and brain abscess of one month's duration. The family history was noncontributory, as was the past history, except for the fact that he had had a draining right ear for 18 months. The present illness had begun on September 8, 1940, with otalgia and the appearance of a yellow discharge from the ear. The clinical course of the disease is illustrated in figure 1. Four days later his physician performed a right myringotomy. Mastoidectomy was performed 72 hours later because of the development of fever and headache. Granulations on the dura and an epidural abscess were found and drained, but no thrombosis of the lateral sinus was demonstrated. The temperature returned to normal for a brief period, then became markedly elevated and the blood culture was positive for a streptococcus with alpha hemolysis. The mastoid was reëxplored and a large abscess of the temporal lobe was exposed and drained. The spinal fluid obtained by lumbar puncture was normal and cultures sterile.

Eight grams of sulfathiazole were administered daily by mouth for 10 days after operation. His temperature returned to normal and he was greatly improved. During this period he received six transfusions of whole blood. Two days after the cessation of the drug the temperature again became elevated, headache and vomiting developed, and he was transferred to the Stanford University Hospitals.

The physical examination revealed a well developed young man who was conscious and well oriented. The temperature was 39° C., the pulse 90, the respirations 22 per minute, and the blood pressure 120 mm. Hg systolic and 70 mm. diastolic. Examination of the eyes showed that the left pupil was larger than the right but both reacted to light and accommodation, while in the fundus papilledema of 3 diopters was observed. The brain was found to be herniating into the right mastoid wound. The mouth and nasopharynx were normal and the neck was slightly stiff; the heart, lungs and abdomen were not remarkable. The extremities showed no abnormalities and the neurological examination was within normal limits.

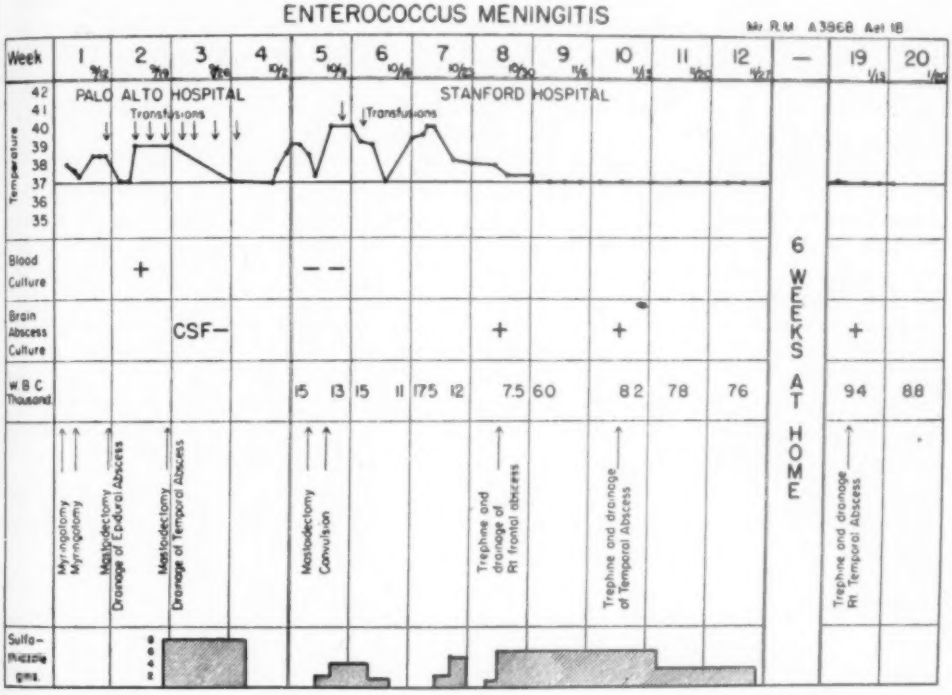

FIG. 1.

Laboratory studies showed the red count to be 4,670,000 and the hemoglobin 82 per cent (Sahli), the white blood count 15,000 per cubic millimeter with 75 per cent polymorphonuclears, 18 per cent lymphocytes and 7 per cent mononuclears. The urine was normal. The second day a very radical mastoidectomy was performed and part of the brain which herniated into the wound was removed with the electrocautery. Two days later he suffered a typical Jacksonian seizure which began in the left foot and became generalized. During the following week 4 grams per day of sulfathiazole were administered by mouth, and the powdered drug was blown in the mastoid wound. Gradual improvement followed and the temperature approached normal. Ventriculography was performed on November 1 because of continuing headache, and the signs of a mass in the right frontal lobe were demonstrated. A large abscess was discovered in this area through a trephine opening, and 75 cubic centimeters of thick pus were evacuated from which a streptococcus with alpha hemolysis was obtained in pure culture.

Six grams of sulfathiazole were administered daily by mouth for the following three weeks and then 3 grams per day for two weeks. The general physical condition improved steadily but on November 15 it was felt that another abscess might be present in the right temporal area, and a collection of pus from which a similar streptococcus was obtained in culture was evacuated through a trephine opening in this region. From this time on clinical improvement was striking, and the patient left the hospital on December 3, apparently well.

On January 13, 1941, he returned to the hospital having had a convulsion 24 hours earlier. Physical examination was within normal limits except for a tender area in the right temporal region, the temperature being 37.8° C., pulse 80, the leukocyte count 9,400 and the hemoglobin 86 per cent (Sahli). An opening was made through the skull over the right ear at the point of greatest tenderness, and a thick-walled abscess was discovered. This was drained and explored, and no connection was found with any of the previous abscesses. No sulfonamides were administered. His postoperative course was uneventful and he left the hospital on January 20. When last seen on January 29, 1941 he appeared to be absolutely well.

Bacteriology. The organisms isolated from the blood and from meningeal abscesses on three occasions appeared to be identical. These streptococci grew in rough colonies on blood agar and formed large areas of bright green alpha hemolysis. They grew well at temperatures of 10° C. and 45° C. in the presence of 6.5 per cent sodium chloride and .10 per cent methylene blue. Gelatine was not liquefied. The antigen obtained from these organisms formed a precipitate in the presence of serum of the Lancefield Group D. These were the biological and serological criteria for the identification of the enterococci as described by Sherman.[14]

Comment. The inclusion of this case under the general classification of meningitis is open to some question since there was never a diffuse or generalized involvement of the meninges. At operation, however, none of the localized abscesses penetrated the cerebral cortex. In every instance the infection lay immediately beneath the dura mater and may be properly classified as a localized, subacute meningitis.

An otitis media provided the portal of entry, and the presence of a positive blood culture early in the illness indicates a widespread dissemination of the organisms. Later there was localization in circumscribed areas of the meninges. At operation it was felt that these collections of pus were not all connected, but this is not susceptible of proof.

The organism isolated from the blood and meninges is not identical with the enterococci derived from the normal stool, but the biological and serological reactions were typical of this group of streptococci as described by Sherman.

Enterococci have been notably resistant to sulfonamide therapy [17] and sulfathiazole has been shown [18] to have very little more effect in urinary tract infections due to these organisms than the earlier drugs. The response to chemotherapy in this case was not dramatic, although it may have assisted in carrying the patient over the earlier acute phase. Drainage of the mastoid bone and local abscesses was necessary before cure was effected.

Case 3—Lancefield Group H Meningitis. Mrs. C. J., a 65-year-old white female housewife, entered the hospital August 3, 1940, with a complaint of headache and

stiff neck of 48 hours' duration. The family history was unimportant as was the past history, except for the fact that she had suffered from sinusitis for many years and had undergone left simple antrotomy in 1925. The present illness began four days before entry with the development of an acute upper respiratory infection with headache which was diagnosed by her physician as acute frontal and maxillary sinusitis. Her clinical course was uneventful until the day before entry when her temperature rose to 100.2° F., and headache and dizziness developed. Within a short time stiff neck appeared, she became irrational and was brought to the hospital. Physical examination revealed a flushed, stuporous, elderly woman. The temperature was 40.2° C., the pulse 120 per minute, the respirations 24 per minute, the blood pressure 132 mm. Hg systolic and 76 mm. diastolic. No tenderness, edema or evidence of periostitis was demonstrated over the paranasal sinuses. The examination of the eyes revealed right lateral rectus weakness, but the pupils were equal in size, reacted to light and accommodation, and the fundi were normal. No abnormalities were seen in the mouth or nasopharynx. The neck was very stiff. The chest was clear to auscultation and percussion; the heart was of normal size, with regular rhythm, and no murmurs were heard. The abdomen was not remarkable. Moderate general motor weakness of the extremities was present; the Kernig sign was positive; the reflexes were sluggish but sensation was intact. The laboratory studies showed a hemoglobin of 88 per cent (Sahli), a red blood count of 5,200,000, a leukocyte count of 15,600 of which 66 per cent were polymorphonuclears, 29 per cent lymphocytes and 5 per cent monocytes. The Wassermann reaction was negative, the urine normal, and the blood culture sterile. Spinal puncture was performed immediately after admission; the pressure was found to be 120 millimeters of water and the dynamics were normal. Twenty-four hundred cells were present, of which 89 per cent were polymorphonuclear leukocytes and 11 per cent lymphocytes. The protein content was 21.2 milligrams. Cultures revealed an alpha hemolytic streptococcus. The patient's hospital course is shown in figure 2.

Twenty grams of sulfanilamide were administered by mouth in the first 72 hours. During this interval the temperature remained elevated and a lumbar puncture revealed spinal fluid essentially similar to that obtained two days before. The concentration of sulfanilamide was 11.7 milligrams per 100 cubic centimeters. Sulfapyridine therapy was instituted at this time and within 24 hours striking improvement had occurred. The cerebrospinal fluid showed a striking fall in total cell count, a rise in glucose content, and the cultures became sterile. Drug therapy was continued for nine days in gradually decreasing dosage. Her hospital course during this time was uneventful except for the development of a moderate secondary anemia which was combated by transfusion of whole blood. Cerebrospinal fluid obtained upon the eighth hospital day was practically normal. Two sharp rises in temperature in the third and fourth weeks were believed to be due to reactivation of her sinus infection. It was, therefore, determined to undertake radical antrotomy, ethmoidectomy and sphenoidectomy. This operation was performed on the left in the fifth hospital week. When the sphenoid sinus was opened it was discovered that an imperfection existed in its roof so that only the mucous membrane separated the sinus from the dura mater. This area was regarded as the probable site of extension of the infection to the meninges. A large opening was provided from this region into the nose in the hope that subsequent difficulties might be avoided. Her postoperative convalescence was uneventful. She left the hospital near the end of the seventh week, and when last seen, four months later, was in good health.

Bacteriology. The organism isolated from the spinal fluid was an alpha hemolytic streptococcus which formed small smooth colonies on blood agar plates. It failed to grow at 10° C. and 45° C. in the presence of 6.5 per cent sodium chloride or .10 per cent methylene blue. When studied by a modification of the Lancefield technic precipitate was formed with Group H serum.

Comment. This is a case of meningitis due to an alpha hemolytic member of the Lancefield Group H. Such strains have been previously described.[19] An infection of the sphenoid sinus was followed by direct extension to the meninges.

Sulfanilamide therapy was instituted without decisive effect on the disease; the patient remained very ill, the spinal fluid was purulent, and the cultures positive. Sulfanilamide content of the fluid was 11.7 milligrams per 100 cubic centimeters. A change to sulfapyridine was made and within 24 hours the temperature was normal, the fluid practically clear, the culture sterile, and the glucose content normal. An uneventful recovery was made except for the complications of operative interference in the sinuses.

It therefore appears that sulfapyridine was a more effective agent in this case of *Streptococcus viridans* meningitis than was sulfanilamide.

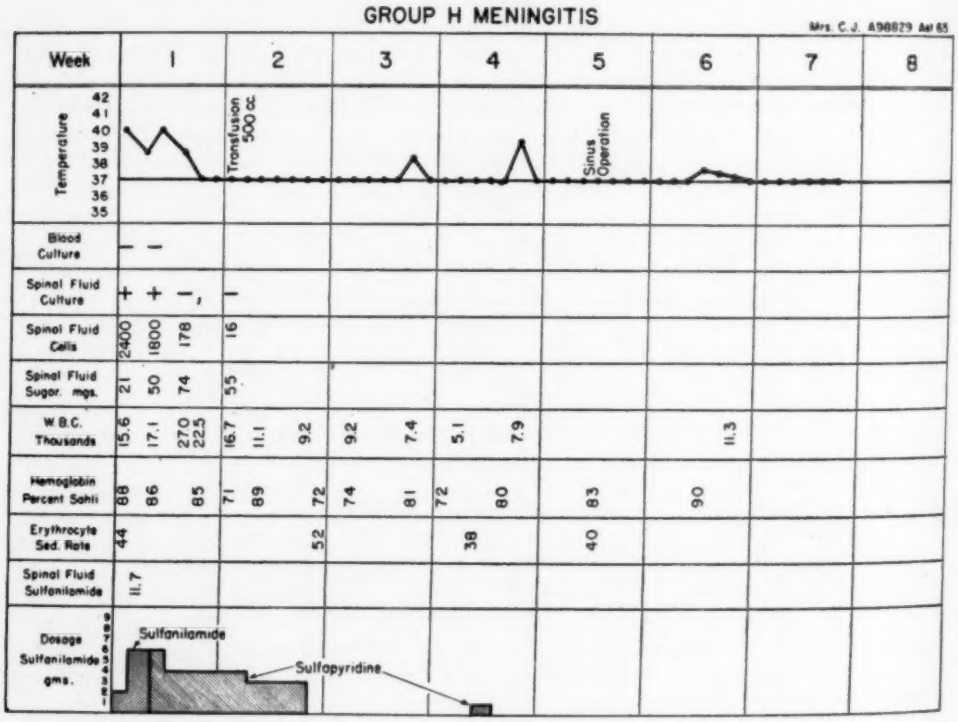

FIG. 2.

Case 4—Lancefield Group F Meningitis. Mr. L. M., a 52-year-old white male kitchen helper, entered the San Francisco Hospital September 5, 1940, with a complaint of swelling of the right cheek for six days. The family history and past history were noncontributory. He had been troubled by pain in the right cheek for two weeks before his entry into the hospital. Seven days before entry he had had a right upper molar extracted, following which swelling had become more marked and very painful. For three days he had suffered from diplopia and had felt feverish. On physical examination he appeared acutely ill; temperature was 103° F., pulse 90

per minute, the respirations 30 per minute. The skin was warm and clear and no petechiae were seen. The pupils were equal in size and reacted to light and accommodation. The lateral rectus muscle of the right eye was paralyzed; the ocular fundi were normal. There was a large tender swelling in the region of the right parotid gland. The ears were not remarkable. The right Stenson's duct was observed to be inflamed and purulent material was expressed from it by pressure over the parotid mass. The nasopharynx was normal and the neck was not stiff. Examination of the chest revealed moist râles and dullness at the right base posteriorly. The heart was not enlarged; rhythm was regular and no murmurs could be heard. The blood pressure was 120 mm. Hg systolic and 75 diastolic. The liver extended 8 centimeters below the right costal margin; the spleen was not felt. The genitalia were normal, as were the extremities. Kernig's sign was not elicited. Laboratory examination of the blood showed a red blood count of 4,820,000, hemoglobin of 98 per cent (Sahli), and leukocyte count of 18,550 of which 78 per cent were polymorphonuclears, 18 per cent lymphocytes, 4 per cent monocytes. The urine was normal, the Wassermann reaction negative. Roentgen-rays of the skull and chest showed no abnormalities. Culture of the blood revealed streptococci with alpha hemolysis. He remained in the hospital five days, the clinical course being illustrated in figure 3.

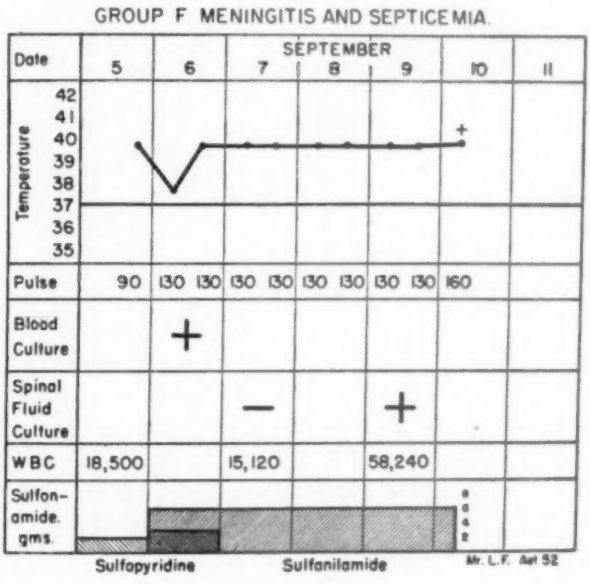

FIG. 3.

Five grams of sulfapyridine were administered by mouth in the first 24 hours followed thereafter by 1 gram of sulfanilamide every four hours for the duration of his disease. On the second hospital day he became comatose, the neck definitely stiff and Kernig's sign positive. Lumbar puncture at this time revealed a cloudy fluid containing 850 cells per cubic millimeter of which 96 per cent were polymorphonuclears. Culture of this specimen showed no growth but that of one obtained two days later showed a streptococcus with alpha hemolysis similar to that obtained from the blood culture.

In spite of intensive supportive therapy the patient became more deeply comatose, temperature and pulse remained elevated, the leukocyte count increased to 58,000 cells per cubic millimeter, and he died September 10, 1940.

Bacteriology. The organism obtained in the blood and spinal fluid was a streptococcus which formed green pigment on blood agar. It failed to grow at 10° C. and 45° C. in the presence of 6.5 per cent sodium chloride and .10 per cent methylene blue. Its antigen precipitated strongly in the presence of serum of the Lancefield Group F.

Comment. This is a case of fatal sepsis and meningitis caused by an alpha hemolytic member of the Lancefield Group F. Members of this group have usually been regarded as frankly hemolytic but Hare [19] has shown that, of a group of strains of streptococci from the nose and throat which failed to form soluble hemolysin, 25 per cent were in Group F and 50 per cent in Group H.

Extension of infection following extraction of a tooth with cellulitis of the face, parotitis, sepsis and meningitis was the course of events in this case. The means by which the infection was transmitted to the meninges is not clear.

Sulfanilamide was the therapeutic agent used. From the experience of case 3 it seems very possible that sulfapyridine or perhaps sulfathiazole would have offered a greater possibility of a satisfactory result. The presence of extensive cellulitis of the face and septicemia would have made the prognosis very grave under any circumstances.

Discussion

These cases are presented for the purpose of emphasizing certain facts. The first is that the streptococci etiologically concerned in meningitis may be shown to be of many distant varieties when studied by suitable biological and serological methods. Evidence is presented from the literature which indicates that 80 per cent of the strains of streptococci isolated from cases of meningitis are hemolytic and practically all of these are members of the Lancefield Group A. Case 1 indicates that other types of hemolytic streptococci may occasionally invade the meninges. It is possible that certain cases in which these more unusual groups of organisms are involved have a milder clinical course, since the patient presented here was recovering before chemotherapy was instituted. It is, therefore, suggested that some of the previously reported instances of spontaneous recovery might have been caused by such organisms.

Secondly, it is apparent from the bacteriological studies on the three strains of non-hemolytic streptococci isolated from cases 2, 3 and 4 that widely different organisms were involved. It is important to bear in mind that such differences exist among the members of the non-hemolytic streptococci in order that suitable studies may be performed which will enable correct therapeutic and prognostic inferences to be accumulated and evaluated.

Chemotherapy appears to have been of very real value in case 3. A dramatic clinical improvement followed the change from sulfanilamide to sulfapyridine. In cases 1 and 2 the effect of the use of sulfonamides was much less clear but it is probable that they were of some help. Death occurred in case 4, but it is important to point out that sulfanilamide was used rather than sulfapyridine or sulfathiazole. This evidence suggests, and an analysis of the few previously described cases partially confirms the fact that sulfapyridine has a very definite therapeutic effect in cases of non-hemolytic or *Streptococcus viridans* meningitis. By inference with the results obtained in other infections sulfathiazole should be of equal value if a sufficient concentration can be maintained in the cerebrospinal fluid. This is usually accomplished without difficulty. The use of sulfanilamide in such cases appears to be contraindicated as it is probably therapeutically ineffective.

Summary

1. Seventeen per cent of all cases of bacterial meningitis are caused by streptococci.

2. Eighty per cent of these organisms are hemolytic and predominantly members of the Lancefield Group A; 20 per cent are non-hemolytic or form green pigment on blood agar.

3. The mortality rate of meningitis due to both types of organisms is 95 per cent without effective therapy.

4. With the use of sulfonamides the mortality is only 20 per cent.

5. Four cases of meningitis due to unusual streptococci are presented. The etiological agent in one was a hemolytic streptococcus of the Lancefield Group B, in the second an enterococcus, in the third a non-hemolytic member of Group H, and in the fourth a non-hemolytic member of Group F.

6. Recovery occurred in three cases and death in one.

7. Sulfonamides exerted a doubtful effect on two cases and brought about dramatic improvement in a third treated with sulfapyridine. Sulfanilamide failed to influence the course of the fatal case.

8. Sulfapyridine is a definitely effective agent in non-hemolytic or "viridans" streptococcal meningitis. Sulfathiazole may also be of value.

9. Sulfanilamide is contraindicated in these infections.

Acknowledgment

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RECENT ADVANCES IN THE CARE OF THE COMATOSE PATIENT *

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THE comatose patient, regardless of the cause of the coma, requires special therapeutic consideration. Coma does not merely indicate an advanced stage of the underlying disease but also complicates it because unconsciousness adds its own characteristic burdens to those of the primary disease. The coma which is of interest to us is that degree of unconsciousness in which the protective reflexes are decreased or absent. The severity of the physical changes which are the sequelae of coma is directly in proportion to the depth and duration of the coma. Because of the opportunities provided by his daily contacts with unconscious patients, the anesthesiologist is able to make many observations which are widely applicable to a general consideration of the state of coma. The patient who is long maintained in an unconscious condition by barbiturate poisoning or an eight-hour inhalation anesthesia for brain surgery—these comatose states offer the anesthesiologist an extensive proving-ground for the evaluation of measures designed to protect and care for the unconscious patient. It is because of these experiences and the emphasis on training in applied pharmacology and physiology of the most direct type seen anywhere in the clinical practice of medicine that the anesthesiologist has become, of late, a valuable member of the hospital team faced with the problem of the comatose patient.

The unconsciousness of the patient adds a tremendous burden to the therapeutic load carried by his physician for he must actively attend to almost every vital function; more specifically, respiration, body temperature, the intake of fluid, minerals and vitamins, excretion and peripheral circulation.

Let us consider each of these functional requirements in turn.

Urinary excretion is of great importance and demands detailed consideration of the fluid and mineral intake as well as meticulous attention to the method and frequency of bladder emptying. We have seen several instances of bladder paresis persist two weeks after a patient had recovered from the unconscious state only because the bladder was permitted to become overdistended and atonic. The maximum volume of a normal bladder is 400 c.c.[1] If catheterization releases a volume much greater than this the patient is likely to develop a hypotonic bladder. When faced by this likelihood the prompt use of bladder contractors, such as prostigmin 1 : 2000 every three hours for five doses, and frequent emptying of the bladder will decrease the number of catheterizations and the tendency toward bladder infection. Delay in emptying the bladder is often due to the physician's desire to decrease the number of catheterizations to minimize urethral and bladder trauma.

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The patient who is likely to remain unconscious for more than six hours should have a retention catheter and the bladder should be emptied every four to six hours, depending on the findings of bladder percussion. A bladder that is percussible or palpable should be promptly emptied. The use of neoprontosil or sulfanilamide in 40 grain doses per day is a valuable prophylactic against urinary infection in patients requiring repeated bladder catheterization or instrumentation.

The urinary output of the unconscious patient should not fall below 1000 c.c. per 24 hours. If this volume is maintained, we may be sure that there is sufficient water in the body to allow efficient temperature regulation and adequate nitrogenous excretion.[2]

Intimately related to the urinary output is the intake of sodium. The presence of an excessive quantity of sodium ions in the tissues inevitably leads to the retention of water to enable the tissue fluids to remain isotonic.[3] This tendency toward keeping the normal status quo of the tissues and blood constant is so vital that it takes precedence over the requirements of the kidneys. Thus, an excessive sodium intake may lead to an inadequate urinary output even though the intake of water would otherwise be sufficient. It is very rare that an inadequate amount of salt is given in the absence of vomiting, diarrhea, hemorrhage, or profuse perspiration. On the other hand, an excessive salt intake is very common in the comatose patient because the daily salt requirement of the healthy adult is only 4–5 gm.[4] and one liter of normal saline contains 9 gm. of sodium chloride. If the salt or saline were administered only by mouth, we might depend on the gastrointestinal mucosa to absorb the needed amount and reject the remainder. Excessive sodium chloride administration by mouth leads only to diarrhea. But the comatose patient receives his fluids by clysis or infusion and the tissues are, therefore, forced to accept the salt and make the best of it by retaining water to keep the tissue fluids and blood at normal osmotic pressure.[4] If kidney function is normal and an abundant amount of "free" water (water not required to maintain normal osmotic pressure) is present, it is possible for the urinary output to rid the body of the excessive number of sodium ions. Very often, however, the renal function in coma, especially in the surgical patient, is also depressed.[4] Thus salt and water retention persists, latent edema increases and, after about five liters of edema fluid have accumulated, there appears obvious evidence of edema, such as pitting on pressure, hydrothorax or pulmonary râles. Salt retention may be so extensive as to lead to a marked increase in blood volume, venous pressure and heart failure. This is very likely to occur when the comatose patient is given desoxycorticosterone acetate (cortate) or whole adrenal cortical extract for the prevention or treatment of shock.[5] We do not decry the use of adrenal cortical extract; in fact, we urge its use.[6] But we wish to spread this warning against the uncontrolled administration of salt and cortical hormones.

If parenteral fluid and saline are administered with the following points in mind there is little likelihood of harm:

(*a*) It is the quantity of sodium ion rather than the quantity of water that determines the occurrence of edema or cardiac overloading.

(*b*) The administration of a liter of 5 per cent glucose in distilled water following each liter of normal saline provides plenty of "free" water.

(*c*) The dehydrated patient has already lost a volume of tissue fluid equal to 6 per cent of his body weight.[7]

(*d*) Every liter of body fluid lost requires replacement with a liter of normal saline.

Edema fluid is most harmful when it accumulates in the viscera of the thorax and least harmful when present in the tissues of the sacral region or lower extremities. Edema fluid is influenced by gravity. The shift of tissue fluid to the pleura and lungs and great veins of the chest decreases the pulmonary vital capacity, increases dyspnea, and favors the appearance of pulmonary edema. It is, therefore, necessary to avoid placing every comatose patient routinely in the horizontal or Trendelenburg posture. In the presence of subcutaneous edema, the semi-sitting position may be advantageously employed if shock, vomiting and profuse bronchial secretions are absent. These symptoms, however, make the Trendelenburg position preferable in spite of its disadvantageous effect of shifting edema fluid to the chest.

It is apropos here to comment that the Trendelenburg position for the treatment of shock is not as beneficial as its universal use might imply. In the therapy of syncope associated with vasodilatation, the common fainting spell, it is of known and proved value.[8] In peripheral circulatory failure associated with spinal anesthesia, the Trendelenburg position has been shown by CoTui to be of very transient and little value. And yet, it is in this type of shock that most surgeons would agree that the Trendelenburg position is indicated. Thus, common usage is no criterion of usefulness. In the prevention or treatment of peripheral circulatory failure due to decreased blood volume, which is the usual and more serious type of shock, it is probably of little value because the maximum mobilization of tissue fluids and pooled blood has already been secured by the operation of more fundamental and effective protective mechanisms such as the contraction of arterioles, veins and venules and the increased osmotic pressure of the concentrated blood always associated with shock.

The characteristic and usually fatal complications of the comatose state (whether the coma is due to alcohol, morphine, ether, cerebral hemorrhage, or pneumonia), if the coma is deep and lasts more than a few hours, are pulmonary edema and pulmonary infection. The factors which favor their appearance are many, so many that in any individual case it is difficult to single out a specific cause. Usually the pulmonary edema and infection are the result of the interaction of several pathological processes. Chief among these causes are:

1. Aspiration
2. Partial respiratory obstruction
3. Generalized tissue edema
4. Shock
5. Anoxia
6. Primary pulmonary infection.

1. The aspiration of saliva and mucus is always to be feared in the unconscious patient, for the laryngeal and cough reflexes, those "watchdogs of the lungs," are usually absent or markedly depressed. Even more likely is aspiration to occur if the patient is vomiting or regurgitating. It is because of this danger that the stomach of the unconscious patient must be kept empty.[9] Even when throat suction is constantly used through an open mouth under direct vision, as in a tonsillectomy under general anesthesia, aspiration occurs in a great majority of cases as was demonstrated by Myerson, who performed bronchoscopic examination routinely on a series of such cases.[10] The presence of stagnant mucus in the tracheobronchial tree is a potent factor in the pathogenesis of pneumonia according to the laboratory studies of Lockwood,[11] and in the production of atelectasis as demonstrated both clinically and experimentally by Coryllos.[12]

2. Partial respiratory obstruction is so easy and common in the anesthetized patient that every anesthetist insists on the use of an artificial airway in the maintenance of deep anesthesia for longer than a few minutes. Coma unrelated to anesthesia is accompanied by the same relaxation of muscle and tissue tone so that there is a great tendency for the respiratory tract to be obstructed by the falling back of the tongue, by the indrawn pharyngeal walls and the partially adducted vocal cords. Should anoxia and tissue edema also be present, then there is added another obstructing factor, swollen pharyngeal and laryngeal walls.[13]

Partial respiratory obstruction leads to pulmonary edema through two mechanisms: (1) Anoxia increases the permeability of the capillaries,[14] including those of the lungs, and the alveoli become filled with a transudate. (2) The "sucking" effect of the marked inspiratory efforts and the increased intrathoracic negative pressure which result from the partial respiratory obstruction. This latter mechanism of causing pulmonary edema has been only recently clearly demonstrated by Barach.[15]

Partial respiratory obstruction in coma must be treated in exactly the same way as in anesthesia, namely, by the insertion of a proper airway. If a pharyngeal airway is insufficient, then an endotracheal tube should be inserted under direct vision laryngoscopy as it is during endotracheal anesthesia. The endotracheal catheter is well tolerated for many hours and even days if its position is not disturbed frequently. The endotracheal tube not only guarantees an open respiratory tract but also prevents the inhalation of mouth secretions and vomitus and facilitates the non-traumatic removal of bronchial

secretions and pulmonary edema by suction through a catheter, easily and frequently inserted into the endotracheal tube.[9, 16]

We wish to note here that the use of atropine in the prevention or treatment of pulmonary edema is illogical. Edema fluid is the result of exudation or transudation and is not the product of glandular secretion. Atropine blocks bronchial glandular secretion but does not affect the exudation or transudation of pulmonary edema. Atropine in the unconscious patient serves only to prevent sweating and thus may interfere with body temperature regulation.

3. Generalized tissue edema of any origin inevitably tends toward pulmonary edema because of the recumbent position of the unconscious patient, the large blood content of the lungs and the vast capillary surface area in the lungs. Of all the organs which edema usually affects, the lungs are the most vital. Recovery from coma is sometimes prevented only by the anoxia caused by pulmonary edema. Oxygen therapy in the presence of gross pulmonary edema is always unsatisfactory unless it is preceded by mechanical clearing of the pulmonary passages.

4. Shock often leads to pulmonary edema and bronchopneumonia because shock is characterized by a diffuse and marked increase of capillary permeability including the capillaries of the lungs. This relationship has been beautifully demonstrated experimentally by the classical work of Virgil Moon.[17] The prevention or treatment of pulmonary edema necessarily involves the prevention or treatment of shock or peripheral circulatory failure. We shall discuss later and at length the subject of peripheral circulatory failure in the comatose patient.

5. Anoxia can be a primary cause of pulmonary edema by its action of increasing capillary permeability. More often, however, anoxia is a secondary and complicating sequel of pulmonary edema, thus tending to perpetuate the pulmonary edema. The anoxia of the comatose patient, to be properly treated, should be differentiated as to its type, i.e., whether the anoxia is of the anemic, histotoxic, stagnant or anoxic group as defined by Barcroft.[18]

6. Pulmonary infection and pulmonary edema are often found together, clinically. Either one may lead to the other. Pulmonary infection promotes pulmonary edema by causing a massive outpouring of inflammatory exudate through the lung capillaries. Pulmonary edema favors infection by providing an excellent culture medium for the bacteria of the tracheobronchial passages and by obstructing the natural clearing mechanisms of the lungs. Just as the obstructed bladder is sure to become the seat of infection so is the obstructed lung certain to develop a pneumonitis. We must adopt the therapeutic attitude of the urologist and always look for and treat any obstructing factors in the lungs, whether it is a mucous plug or edema fluid, when we attempt to prevent or treat a pneumonia.

Morphine has no place in the treatment of pulmonary edema even though

convention has sanctioned it. Morphine anesthetizes the cough reflex, the chief mechanism of the lungs in their effort to maintain an unobstructed airway. This expulsive mechanism is even more important in the stuporous or unconscious patient with pulmonary infection or pulmonary edema.

Stimulants are almost always found listed in the order sheets of every coma case that dies. In fact, they are so frequently used as a last-hour desperate measure that the term "medical last rites" has been applied to this usually hopeless and often harmful series of injections of coramine, epinephrine, strychnine, caffeine, digitalis, etc. Many physicians have considered such drugs as coramine and strychnine to be valueless under all circumstances because they have always used these drugs on terminal cases or on improper indications. The manufacturers of such drugs as coramine or metrazol are partly to blame for this therapeutic nihilism because they have been guilty in the past of encouraging the indiscriminate use of their products. The chief reason, however, for the incorrect use of stimulants in comatose patients is a lack of correct pharmacological understanding of the relationship of the large variety of stimulants to coma.

(*a*) The analeptic stimulants, namely, coramine, metrazol and picrotoxin, are chiefly of value in combating coma due to the depressant drugs, e.g., morphine, barbiturates, paraldehyde, chloral hydrate, etc.[19, 20] In these drug-produced comas we can obtain brilliant results, as, for example, in the following case.

A 28-year-old eclamptic was delivered by caesarean section but continued on to have two more convulsions in the next six hours. In the first 12 hours after operation she received two doses of morphine sulphate grain ¼, 2 c.c. of 50 per cent magnesium sulphate by hypodermic and 30 grains of chloral hydrate by rectum. She was mildly cyanotic despite oxygen therapy, breathed rapidly and shallowly; the lungs were filled with loud bubbling râles; blood pressure was 80 mm. of Hg systolic and 40 diastolic, and she was deeply comatose. Her depressed central nervous system and peripheral circulatory system were regarded by her attending physician as terminal events. But the anesthesiologist considered her coma to be only in part due to exhaustion following convulsive activity and that the depressant drugs administered for control of eclampsia were also responsible for her depressed state. The intravenous injection of 3 c.c. of coramine produced an immediate and marked stimulation of restlessness and pharyngeal reflexes. After a few minutes her condition returned to its previous status but the repetition of intravenous coramine, 3 c.c., secured immediate awakening, mumbling speech and marked restlessness; and the blood pressure rose to 110 systolic and 60 diastolic. She was out of danger within 12 hours. Of course, other therapeutic measures advised in this paper were also used, such as aspiration of the trachea, the insertion of an airway, and the inhalation of 100 per cent oxygen.

(*b*) The sympathico-mimetic stimulants, such as epinephrine and ephedrine, are indicated in the comatose state associated with Stokes-Adams seizures, allergic attacks or extensive vasodilatation as in ordinary syncope, spinal anesthesia or excessive drug depression.[20] These drugs are not only effective peripheral vasoconstrictors but also possess some of the cerebral

awakening and respiratory-stimulating qualities of the above mentioned analeptics.[21] In fact, the analeptic and sympathico-mimetic drugs are more effective when employed synergistically in coma caused by excessive doses of hypnotics or narcotics.[20]

(*c*) The purine group of stimulants, namely, caffeine and theophylline, are of little value in coma except for the parenteral use of caffeine in lowering intracranial pressure and the intravenous injection of aminophylline for the correction of asthmatic [22] and Cheyne-Stokes types of breathing.

(*d*) Strychnine is an unusual stimulant in that its predominant effect is on the spinal cord in which it increases irritability by lowering the synapse threshold. Its chief value lies in a marked ability to increase the tone of the voluntary musculature, as demonstrated by Yandell Henderson.[23] This drug is most useful for the prolonged maintenance of good muscular tone in the comatose patient threatened with peripheral circulatory collapse due to a decreased supportive action of relaxed musculature on the intramuscular capillary and venous blood vessels.

The dose and method of administration of stimulants are very important in obtaining the best results in coma. The intravenous route is preferred because the desired results are obtained immediately and dosage can be more promptly and accurately judged. Coramine 5 c.c., metrazol 3 c.c., or picrotoxin 1 c.c., are the initial intravenous doses; they should be repeated every 15 minutes until the desired increase in reflex and cerebral activity is seen. Facial twitching is the first sign of maximum effect and it must be allowed to disappear before continuing with the stimulant.

Epinephrine is usually given in overdosage. Two or three minims intravenously or 4–5 minims hypodermically is sufficient in the great majority of instances. The toxic effects of epinephrine on the heart have not been sufficiently appreciated.[24] Ephedrine sulphate ½ c.c. (25 mg.) intravenously is safer and longer-lasting than epinephrine.[25] Neosynephrine ¼ c.c. intravenously or ½ c.c. hypodermically is an excellent long-acting sympathetic stimulant which has the least disturbing effect on the cardiac rhythm or the cerebral cortex.[26] It is the sympathetic-stimulating drug of choice in the presence of cardiac disease. The excessive use of vasoconstricting agents is capable of causing shock by producing so intense an ischemia as to cause capillary damage.[27] They are indicated in peripheral circulatory depression caused by depressant drugs or primary vasodilatation; they are contraindicated in hemorrhage or "secondary" shock.

Strychnine sulphate is rarely used in sufficient amounts to secure a therapeutic effect. The minimum dose is $\frac{1}{30}$ grain repeated every four hours.

The comatose patient usually dies in peripheral circulatory failure with pulmonary edema and infection as terminal manifestations. The comatose state favors the appearance of peripheral circulatory failure because there is

a widespread lowering of the muscular and tissue tone accompanying the severe central nervous system depression. All measures which increase muscular tone, such as strychnine, carbon dioxide inhalation, muscular activity and bandaging of the extremities, prevent the pooling of blood and tissue fluid in the tremendous capillary network of the muscles. The increased practice of measuring hemoconcentration should enable the clinician to begin shock therapy before the arrival of the relatively late sign of low blood pressure. The prophylaxis of decompensated shock is far easier and more effective than the treatment of obvious peripheral circulatory collapse. In the treatment of this condition we should depend more on intravenous saline, blood plasma and adrenal cortical extract than on epinephrine and other attempts to cause vasoconstriction in a patient whose vasoconstricting mechanism is operating at its maximum.

The central nervous system that is depressed is in need of increased oxygen irrespective of the cause of the coma. Space does not permit us to recite the results of the detailed studies of brain metabolism in the various types of coma, but it suffices to state that we may always expect that there is deficient oxygen delivery by the blood or uptake by the brain cells in coma. In the face of this derangement of oxygen metabolism the least that the clinician can do is to supply a maximum amount of oxygen. The inhalation of 100 per cent concentration of oxygen supplies the maximum amount of oxygen. This is not harmful when continued for not more than 12 consecutive hours, and it may be repeated for periods of 12 hours each when the administration is alternated with four hour periods of 50 per cent oxygen.[28] It seems to us that this dosage of oxygen is indicated in every case, for even a normal individual breathing 100 per cent O_2 absorbs an increased amount of oxygen into solution so that the total oxygen content of arterial blood is increased by 10–15 per cent (2.5 c.c.).[28] The use of a B–L–B or similar type of face mask enables one to give high concentrations of oxygen in a very effective and economical way.[29]

Summary

With the increased tendency of physicians to secure special training in anesthesiology and to study the physiology and pharmacology of the unconscious patient, we have witnessed many recent advances in the clinical care of all comatose patients. We have learned to detect early in the comatose patient the many abnormalities of the respiration, circulation, excretion, and salt and water metabolism. A valuable set of clinical measures, solidly grounded on scientific studies, is now available. The comatose patient has a more hopeful prognosis than ever before. If the physician approaches the comatose patient in a spirit of energetic optimism which encourages him to apply vigorously the measures recommended in this paper, many surprising and happy recoveries may be obtained in situations usually considered hopeless.

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THE CONCENTRATION OF CREATINE IN HEART, DIAPHRAGM, AND SKELETAL MUSCLE IN UREMIA *

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THE rôle of creatine in muscle metabolism has been well established. All voluntary muscles of vertebrates are rich in creatine, whereas smooth muscle contains relatively little. Muscle efficiency stands in a definite relationship to the amount of creatine present.

Numerous investigators have determined the creatine content of heart and skeletal muscle. As early as 1913 Myers and Fine [1] reported on muscle

TABLE I

Creatine Values of Human Muscles in Health and in Disease Obtained by Various Investigators

Investigators	Muscle Studied	Creatine Values in mg. per cent
Denis	Psoas	360–421
Bodansky	Diaphragm, normal	309–331
Bodansky	Heart, normal	220
Bodansky	Psoas, normal	485
Seecof, Linegar and Myers	Left ventricle, normal	Range 150–300, average, 211
	Right ventricle, normal	Range 100–200, average, 148
	Pectoralis major, normal	Range 258–564, average, 394
Cowan	Heart, normal	202 ± 37
	Heart in pyelonephritis, uremia, bronchopneumonia and sepsis	117
	Heart in malignancy	117–134
	Heart in cardiac decompensation	144
	Heart in hypertrophy without decompensation	165 ± 30
	Heart in chronic nephritis	144–172
Herrmann, Decherd and Oliver	Left ventricle normal	175 ± 21
	Heart disease without failure	173
	Heart in hypertension without failure	198 ± 16
	Heart in coronary sclerosis	157
	Left ventricle in glomerulonephritis and uremia	159
	Left ventricle in anemia	157
	Heart in prolonged infections	119
	Left ventricle in congestive failure	122

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From the Medical Division and Division of Laboratories, Montefiore Hospital for Chronic Diseases, New York City.

TABLE I—*Continued*

Investigators	Muscle Studied	Creatine Values in mg. per cent
Bodansky and Pilcher	Normal left ventricle	Range 38–295, average 159
	Normal right ventricle	Range 38–230, average 114
	Left ventricle in congestive failure	Range 38–265, average 139
	Right ventricle in congestive failure	Range 38–230, average 103
	Cardiac hypertrophy, left ventricle	Range 81–237, average 146
	Cardiac hypertrophy, right ventricle	Range 49–169, average 109
	Minimal heart disease, left ventricle	Range 97–273, average 175
	Minimal heart disease, right ventricle	Range 84–212, average 128
Linegar, Frost and Myers	Left ventricle, normal	200
	Right ventricle, normal	150
	Pectoralis major, normal	400
	Left ventricle, cardiac decompensation	175
	Right ventricle, cardiac decompensation	132
	Pectoralis major, cardiac decompensation	390
	Diabetes, left ventricle	195
	Diabetes, right ventricle	143
	Diabetes, pectoralis major	313
	Left ventricle in carcinoma	180
	Right ventricle in carcinoma	129
	Pectoralis major in carcinoma	340
	Left ventricle in uremia	287
	Right ventricle in uremia	210
	Pectoralis major in uremia	501
	Left ventricle in uremia with heart failure	176
	Right ventricle in uremia with heart failure	136
	Pectoralis major in uremia with heart failure	401
Constabel	Heart, normal	170–180
	Heart, fatty	60–120 rt. and lt. ventricle
	Heart, malignancies	70–100
	Heart, tetanus	80
	Heart, osteomyelitis	170–180
	Heart, kidney abscess	160
	Heart, puerperal sepsis	188
Myers and Fine	Abdominal muscle in peritonitis	396
	Leg muscle in sarcoma of leg	391

creatine under normal conditions. They established the fact that urinary creatinine and muscle creatine are interdependent in a given species. Denis,[2] in 1916, studied the creatine content of normal psoas muscle.

Constabel,[3] in 1921, was the first to determine the creatine content of human heart muscle. He found this to be 170–180 mg. per cent for the

left ventricle, whereas it amounted to only 130 mg. per cent for the right ventricle. Age and sex appeared to play no rôle. According to Seecof, Linegar and Myers [4] both ventricles show the same creatine concentration at birth, but a difference in creatine content is established during the first year. Creatine concentration was increased in hearts hypertrophied to a certain degree, but beyond that level it showed a decrease. Linegar, Frost and Myers [5] found the creatine values for the left ventricle higher than those for the right one in a number of species including the human. There was no apparent correlation of creatine content and heart weight but the average was slightly higher for heavier hearts. Creatine content was reduced in muscular exercise, chronic disease and congestive failure; reduced after an initial increase, in fasting; and variable in acute diseases.

Cowan [6] studied the creatine values of 80 hearts, 48 of which were normal, 17 of which were from cases of decompensated heart disease, and 15 from patients with various diseases. Cardiac creatine was reduced in diseases accompanied by muscle weakness, cachexial disease and malignancies, but cases of sepsis showed normal values. He found the creatine content of hypertrophied hearts without failure to be between that of normal and that of decompensated hearts. He was of the opinion, however, that hypertrophied hearts have higher creatine concentrations than non-hypertrophied hearts.

Herrmann, Decherd and Oliver [7] found that in four patients dying after acute coronary thrombosis the infarcted areas showed a striking loss of creatine as compared to the uninfarcted areas, the ratio being about two to one. In the uninfarcted area creatine was reduced to the amount found in congestive heart failure. The average creatine content of the left ventricle in cases of congestive heart failure was 30 per cent less than normal. Bodansky and Pilcher [8] found the most marked variation in creatine content in patients with congestive failure and the least variation in those with minimal heart disease. Conditions burdening one side of the heart (like tuberculosis and pneumonia which predominantly affect the right side of the heart) caused the greatest decrease in creatine in that portion. Linegar, Frost and Myers [5] found that the creatine content of neither voluntary nor cardiac muscle bore any direct relation to creatinine retention in the blood. However, in most cases with low creatine concentration for heart muscle there was heart failure.

Chanutin and Silvette [9] state that in nephritis there is a marked accumulation of creatine as well as creatinine in the blood. Seecof, Linegar and Myers [4] believe that retention of creatinine in renal disease causes a shift of the normal equilibrium between creatine and creatinine toward the creatine side. In this manner they explain the greatly increased concentration of creatine in cardiac and voluntary muscle in their cases of renal disease. The greatest concentration of creatine they found was in the left ventricle and voluntary muscle in two instances of renal arteriolosclerosis with cardiac hypertrophy. Linegar, Frost and Myers [5] also reported high creatine values

for cardiac and voluntary muscle in uremia without heart failure, reaching 500 mg. per cent in voluntary muscle. In uremia with heart failure, creatine content of both the right and left ventricles and the pectoralis major was not as marked as in uremia without heart failure. There was no relationship of creatine concentration of muscle to creatinine concentration and CO_2 combining power of the blood. Herrmann and his co-workers,[7] studying similar material, found low creatine concentrations of muscles. To our knowledge the only determinations of the creatine content of the normal human diaphragm are those of Bodansky,[10] who reported three specimens which showed values ranging from 309 to 331 mg. per cent. Since only these few figures were available, we estimated the creatine content of the diaphragm in normal human beings. Thus we were able to gauge the effect of uremia on the storage of creatine in the diaphragm. The normal diaphragms of 12 males and three females were obtained with one exception within 24 hours of death. In the majority of cases death was the result of accident or assault so that the tissues were as nearly normal as possible. Except for one specimen from a male child eight years of age, all were from adults.

TABLE II

Glomerulonephritic Group

Sex	Age	Primary Disease	Maximum Blood Chemistry Findings in mg. per cent
F.	20	Chronic glomerulonephritis, hypertension, uremic pericarditis with effusion	Urea N 104 Creatinine 8.3 CO_2 35 vol. %
M.	25	Chronic glomerulonephritis, congestive heart failure with ascites and bilateral hydrothorax	Urea N 211 Creatinine 10
M.	44	Hypertension, diabetes mellitus, chronic glomerulonephritis, congestive heart failure	Urea N 108
F.	56	Chronic glomerulonephritis, hypertension, diabetes, congestive heart failure	Urea N 75.6
M.	69	Chronic glomerulonephritis, hypertension, myocardial infarction, congestive heart failure	Urea N 157.2 CO_2 32 vols. % Creatinine 2.7
M.	20	Chronic glomerulonephritis, hypertension	Urea N 115 Creatinine 6.5 CO_2 41 vols. %
M.	18	Chronic glomerulonephritis, terminal congestive failure	Urea N 202 Creatinine 15 CO_2 24 vols. %
F.	60	Chronic glomerulonephritis, diabetes, congestive failure 2½ years	Urea N 81.6 Creatinine 4.6 CO_2 36 vols. %

TABLE II (*Continued*)

Glomerulonephritic Group

Creatine, mg. per cent			Heart Weight at Necropsy in Grams	Cause of Death
Heart	Muscle	Diaphragm		
116	312	183	300	Uremia
106	282	237	525	Uremia
68	—	70	410	Uremia
111	76	70	320	Sepsis Uremia
82	185	—	525	Uremia
113	395	246	500	Diffuse broncho-pneumonia
101	—	—	1770	Uremia
212	—	—	385	Infection and uremia

TABLE II (*Continued*)

Renal Arteriolosclerosis

Sex	Age	Primary Disease	Maximum Blood Chemistry Findings in mg. per cent
F.	48	Rheumatic mitral stenosis and insufficiency, hypertension, renal insufficiency, congestive heart failure	Urea N 86.5 Creatinine 2.1
F.	69	Hypertension, hemiplegia, renal insufficiency	Urea N 47.2
F.	81	Ulcers of leg, renal insufficiency one month	Urea N 101 Creatinine 4.4
M.	62	Rheumatic mitral and aortic disease, angina pectoris, congestive heart failure 7 years, syphilis	Urea N 82 Creatinine 2.1
F.	58	Hypertension, diabetes 10 years, congestive heart failure 5 years	Urea N 87.5 CO_2 30 vols. %
M.	62	Hypertension 5 years, hemiplegia one year before admission	Urea N 155 Creatinine 2.1
M.	52	Rheumatic mitral and aortic disease, anginal and progressive congestive failure 5 years	Urea N 209 Creatinine 6 CO_2 10 vols. %
F.	49	Hypertension, cardiac enlargement, congestive failure, malignant renal hypertension	Urea N 50 Creatinine 3.7

TABLE II (*Continued*)
Renal Arteriolosclerosis

Creatine, mg. per cent			Heart Weight at Necropsy in Grams	Cause of Death
Heart	Muscle	Diaphragm		
65	96	107	650	Uremia
198	—	190	340	Sepsis
106	—	97	350	Uremia
67	—	42	920	Progressive congestive ht. failure
113	—	97	640	Cerebral insult
139	—	148	500	Uremia, recent myocardial damage
93	370	210	650	Uremia
151	300	183	—	Uremia

TABLE II (*Continued*)
Renal Obstruction

Sex	Age	Primary Disease	Maximum Blood Chemistry Findings in mg. per cent
F.	65	Carcinoma of stomach with generalized abdominal metastases	Urea N 83.3 Creatinine 4.5
M.	52	Carcinoma of stomach with metastasis	Urea N 146 Creatinine 2.7
M.	54	Carcinoma of bladder with extension to pelvis, bilateral hydroureter and hydronephrosis	Urea N 147
F.	41	Carcinoma of breast with metastasis, metastasis to lungs, liver, spine	Urea N 100 Creatinine 5.3
M.	62	Multiple myeloma with metastasis to ribs, right kidney, lymph nodes. Chronic nephritis, hypertension	Urea N 129 Creatinine 5.3
F.	55	Renal tuberculosis, post. right nephrectomy, left kidney and ureter tuberculosis	Urea N 167 Creatinine 7.5
M.	69	Chronic pulmonary, ileal, renal, ureteral and bladder tuberculosis, bilateral renal calculi	Urea N 75.5 Creatinine 2.2
M.	35	Tuberculosis, pyelonephritis, ureteritis and cystitis, tuberculosis of the liver, lungs, spleen and prostate	Urea N 160 Creatinine 7.5 CO_2 15 vols. %
F.	40	Nephrolithiasis, pyelonephritis, contracted kidney, ureteritis cystica	Urea N 129 Uric acid 9.5 Creatinine 8.7
F.	54	Bilateral congenital polycystic kidneys, cysts of liver and suprarenals	Urea N 260 Creatinine 4.6

TABLE II (*Continued*)

Renal Obstruction

Creatine, mg. per cent			Heart Weight at Necropsy in Grams	Cause of Death
Heart	Muscle	Diaphragm		
157	155	240	250	Uremia
156	223	192	300	Uremia
185	—	102	210	Bronchopneumonia
98	308	195	330	Left ventricular failure
129	362	388	300	Uremia
142	297	210	340	Sepsis
113	276	210	280	Uremia
87	—	187	265	Uremia
115	—	—	550	Uremia
138	—	125	240	Uremia

It appeared desirable also to study the creatine content of large and small hearts from uremic patients with and without heart failure. For purposes of comparison we also determined the creatine content of muscles of cases in which the heart was not diseased, as in renal tuberculosis and malignancies with uremia as the result of obstructive phenomena.

Findings. Creatine was determined according to Rose, Helmer and Chanutin.[11] Muscle samples were, in the majority of instances, obtained within 24 hours after death. The material consisted of specimens of heart, diaphragm and skeletal muscle obtained from eight cases of uremia secondary to chronic glomerulonephritis, eight cases of uremia secondary to renal arteriolosclerosis, and 10 cases with obstructive and destructive renal lesions resulting in uremia. Diabetes occurred six times, four times associated with glomerulonephritis and twice with renal arteriolosclerosis. In the obstructive group there were four malignancies, one multiple myeloma, three cases of tuberculosis including renal tuberculosis, one with calculus pyelonephritis and one with bilateral polycystic disease of the kidneys. The features common to all were the existence of chronic diseases and their termination in uremia.

Though grouping is difficult because of the marked overlapping of diseases one may divide the material into the three groups mentioned above. A further classification may then be made on the basis of heart size, congestive failure, cachexial diseases and infection. The difficulty of grouping the cases is increased by lack of knowledge of the causes of variations in

creatine content of the muscles, and of the factors involved in any given instance.

Most of the factors known to produce low creatine values for muscle were present in one or another of our cases. Muscle weakness, chronic disease, chronic infection, malignancy, marked cardiac enlargement, congestive heart failure, cachexia and infection played a part. Severe acute sepsis, another cause of a low creatine value in muscle, was terminal in some instances.

In the group with chronic congestive heart failure the etiological basis was rheumatic heart disease in two cases, essential hypertension in four, and chronic glomerulonephritis in five. All had cardiac enlargement, the usual finding in chronic congestive heart failure, irrespective of the etiological agent. Heart weights ranged from 320 to 1770 grams. The average creatine content of the myocardium was 106 mg. per cent. Although the creatine in the skeletal muscle amounted to 370 mg. per cent in one case, it was low in all the others, with an average of 218 mg. per cent. The highest figure for diaphragm creatine was 237 mg. per cent in one instance, but the average for this muscle was 127 mg. per cent. A relatively high figure for creatine in one muscle did not mean a correspondingly high creatine content in another.

The relationship of relatively small hearts weighing 300 grams or less to the creatine content of muscle is an interesting one. Although creatine figures are generally low, they are considerably higher than in chronic congestive heart failure. Average creatine values were 135, 266 and 203 mg. per cent for myocardial, skeletal and diaphragm muscle respectively. Again, no relationship existed between the creatine figures for one muscle and those for another. The low creatine values may be explained by consideration of the fact that carcinoma occurred four times, advanced renal tuberculosis three times, multiple myeloma, chronic glomerulonephritis and congestive heart failure once each in this group. In addition, Vincent's angina, sepsis and bronchopneumonia were also contributory factors to a low creatine content in several of the cases.

In the group associated with cachexia, consisting of four cases with carcinoma, one with multiple myeloma, and three with tuberculosis, low creatine figures were obtained. The creatine values corresponded to those obtained in small hearts. Since hearts of this size were present in our cases, this may have been a contributory factor. The average for the heart was 133; for skeletal muscle, 270; for diaphragm, 215 mg. per cent. Despite the small hearts and the absence of chronic congestive heart failure, chronic cachexia resulted in low creatine findings in all the muscles studied, even though all these patients showed creatinine retention and uremia.

Five cases, including two with infections severe enough to produce gangrene, died of sepsis. The average creatine content was 170 mg. per cent for the myocardium, 187 for voluntary muscle, and 143 for diaphragm. In

two cardiacs creatine was within normal limits. One of these had been in chronic congestive heart failure and another had had hypertension. Evidently, in exceptional cases, congestive failure may not produce significant or actual decreases of creatine in the myocardium. Possibly creatinine retention in these two instances resulted in normal creatine values.

Four cases with moderate cardiac enlargement with heart weights ranging from 385 to 550 grams had had no congestive heart failure. The average creatine values were 145 mg. per cent for the myocardium, 395 for skeletal muscle, and 197 for the diaphragm. The creatine content in all the muscles studied was slightly but definitely higher than in the group in failure. A contributory factor to low creatine values in this sub-group was the presence of infection in two patients and recent myocardial damage in another.

Since low creatine figures have been reported in the muscles in diabetes, those of six diabetics were analyzed. One had had hypertension; another, rheumatic heart disease; and four, glomerulonephritis. Cardiac enlargement and congestive heart failure were present in every one. Infection complicated the course in two. The average creatine figures were 108 mg. per cent for the myocardium, 119 for skeletal muscle, and 86 for the diaphragm. The highest single figures for creatine in the diabetic group were 185 mg. per cent for voluntary muscle, 107 for the diaphragm, and 212 for heart muscle, although in this case there had been congestive failure. The range of heart muscle creatine in the other five cases was from 65 to 113 mg. per cent. Since all were in congestive failure, it is reasonable to expect such low creatine figures for the myocardium. The lowest figures for muscle creatine in all the groups were obtained in the diabetics. It appears that diabetes per se is a factor lowering the creatine reserves of muscle.

The creatine content of the normal diaphragm ranged from 162 to 288, with an average of 234 mg. per cent.

Table 3 gives a cross sectional summary of the creatine findings in all the sub-groups and in the normal diaphragm.

Discussion

The rôle of creatine in muscular efficiency has been postulated on well established clinical, experimental and pathological evidence. The more active and more efficient muscles in the body have a higher creatine content. The biological difference between the right and left ventricle is confirmed by different quantities of creatine in each. Diseases of the heart and myocardial infarction result in diminished myocardial creatine, especially marked in the infarcted areas. In failure the creatine of both ventricles is greatly decreased. Diseases affecting one side of the heart show a lower creatine concentration in that side. In the presence of low creatine concentration in the myocardium, heart failure is usually present. In our material creatine concentration of the myocardium was low, not only as the result of heart

failure, but apparently as part of a generalized loss of muscle creatine including the heart, due to chronic and wasting diseases. Nevertheless, even in this material, in congestive failure creatine concentration of all the muscles studied was significantly lower than in the group without failure.

There is a well established creatine-creatinine balance in the body. Creatine excretion for a given individual is a fairly constant quantity. However, increase in creatinine is known to cause an increase in creatine in muscle. The highest figures for creatine in cardiac and skeletal muscle have been reported by Linegar and his co-workers [5] in cases showing uremia. When creatine saturation exceeded a certain level in skeletal muscle it was then

TABLE III

Average Creatine Values in Cardiac, Skeletal and Diaphragm Muscles in Various Groups

	Group	Number Analyzed	Mg. per cent
Cachexial diseases	Heart	8	133
	Skeletal muscle	6	270
	Diaphragm	8	215
Congestive heart failure	Heart	11	106
	Skeletal muscle	6	218
	Diaphragm	8	127
Diabetes (all were in failure)	Heart	6	108
	Skeletal muscle	3	119
	Diaphragm	4	86
Enlarged hearts, no failure	Heart	4	145
	Skeletal muscle	1	395
	Diaphragm	2	197
Hearts weighing 300 gm. or less	Heart	8	135
	Skeletal muscle	5	266
	Diaphragm	8	203
Sepsis	Heart	5	170
	Skeletal muscle	2	187
	Diaphragm	4	143
Normal diaphragms		15	234

increased in all muscles, though not uniformly. In uremia plus heart failure, creatine concentration was much less marked. However, like Herrmann and his co-workers,[7] we did not find marked creatine concentration in the muscle in uremia even when creatinine was greatly elevated in the blood. In the absence of failure the creatine of the muscles was higher than in cases showing failure. This difference may be due to the fact that Linegar and his co-workers [5] studied a different type of patient. They had only five cases of uremia and six of uremia with congestive heart failure. We had 26 patients with uremia of whom 11 had congestive failure. Their material was derived from young people; ours was chiefly from patients of advanced age with severe chronic diseases.

Evaluation of the entire series shows that hearts in failure had an extremely low average myocardial creatine content, 106 mg. per cent, and only one had 212 mg. per cent. The enlarged hearts without failure had a slightly higher myocardial creatine content, 145 mg. per cent. The myocardial creatine of the diabetics was extremely low, as was to be expected, since they were all in failure, and the average of 108 mg. per cent corresponds to the average of the cases in failure. Cachexial diseases yielded an average of 133 mg. per cent, but some of these were also in failure. Hearts weighing 300 grams or less had an average myocardial creatine content of 135 mg. per cent which may be due to coexistent chronic diseases including malignancies and tuberculosis. Septic cases showed an average myocardial creatine of 170 mg. per cent, the highest in the entire series.

Creatine in skeletal muscle showed marked variations. Cachexia, with an average of 270 mg. per cent, caused considerable reduction. Congestive failure caused even further reduction to an average of 218 mg. per cent. Diabetes plus congestive failure caused a reduction to 119 mg. per cent, indicating the rôle of diabetes, per se, in lowering creatine reserves. Sepsis caused a reduction to an average of 187 mg. per cent in skeletal muscle.

In cachexias the creatine content of the diaphragm was only slightly decreased, 215 mg. per cent, while it was greatly reduced in the myocardium. In congestive failure the creatine of the diaphragm, 127 mg. per cent, was markedly decreased. In the diabetics 86 mg. per cent were present in the diaphragm. This figure, the lowest for the diaphragm in all the groups, was not surprising since congestive failure and diabetes both played a rôle in decreasing the creatine content. In large hearts without failure the creatine value was 197 mg. per cent, a relatively high figure. In sepsis the average creatine of the diaphragm (143 mg. per cent), as well as that of skeletal muscle, was particularly reduced, though the heart suffered less. It is evident, therefore, that creatine storage in one muscle system is essentially independent of that in another. However, when creatine reserves were greatly depleted in one system, as in congestive failure and in diabetes with congestive failure, they were also greatly depleted in all other muscle systems.

The low creatine figures in all types of muscle and especially in the left ventricle in heart failure may be due either to greater breakdown of creatine or to inadequate resynthesis of this compound. The increased accumulation of lactic acid in heart failure may prevent the proper resynthesis of creatine and thus contribute to low creatine values and to the continuation and augmentation of heart failure. A low creatine reserve persists in diabetes, as shown in this study and by the work of others,[5] but it is as yet impossible to determine the responsible factor.

On the basis of Linegar's [5] work it might have been assumed that the marked nitrogen retention which was present in all our cases would result in creatine retention in all types of muscle. We did not, however, find this to be the case.

The findings presented in this study show a low creatine reserve in cases of creatinine retention associated with uremia. Creatine storage may be depleted or retention offset by congestive heart failure and wasting diseases, despite marked creatinine concentration resulting from uremia.

Summary

1. Creatine determinations were made on the diaphragm, heart and skeletal muscles of 26 patients with uremia. Despite marked creatinine retention associated with uremia the creatine was greatly reduced in all the muscles studied.

2. In uremia associated with chronic congestive heart failure creatine concentration was greatly reduced in all the muscles studied. It appears that congestive failure, diabetes and terminal acute infections cause marked losses of creatine in excess of the possible increase in creatine resulting from creatinine retention. There was no parallelism in creatine loss in heart, diaphragm and voluntary muscles, but when creatine reserves were extremely low in one muscle, they were also greatly reduced in other muscles.

3. Since the lowest figures for the entire series were obtained in the six diabetic patients, who happened also to be in failure, it appears that diabetes is a contributory factor to the reduction of the creatine reserves of all muscles.

4. Patients with enlarged compensated hearts had less marked losses of creatine in heart, diaphragm and skeletal muscles. The loss of creatine reserves appears in these cases to be due to chronic disease, despite the nitrogen retention. The 10 cases with hearts weighing 300 grams or less, and the eight cases of cachectic diseases showed similar findings. The low creatine content in these patients is probably also the result of chronic disease.

5. Creatinine retention in uremia may be expected to cause retention of creatine in muscles and some workers have reported the highest figures for muscle creatine in uremia. Our results, however, do not corroborate these findings.

6. Fifteen normal diaphragms were analyzed. The average creatine content of this muscle was 234 mg. per cent. In chronic diseases and congestive failure, especially in diabetes, the concentration of creatine was greatly reduced in the diaphragm as well as in other muscles.

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OBSERVATIONS ON THE COMPARABLE EFFECTS OF PROTAMINE ZINC AND REGULAR INSULIN IN DIABETIC PATIENTS FOLLOWED OVER A PERIOD OF YEARS *

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In a previous study[1] we reported observations on 20 patients with diabetes mellitus who were followed for periods while on regular insulin and who were then transferred to protamine zinc insulin and observed for periods of eight to 14 months. In this group of patients it was found that four never reacted favorably to protamine zinc insulin, and that after eight months five patients had to be returned to regular insulin alone because of the tendency for the occurrence of severe insulin shock or uncontrolled glycosuria. Of the remaining 11 patients of the group eight required both regular and protamine zinc insulin, while three were adequately controlled on protamine zinc insulin alone. Since that report, which was published in 1938, we have continued to observe most of these patients and have studied an additional number of patients. We are now reporting a group of 34 patients who were kept under observation continuously for periods of from one to five years.

During the past five years there have been a great many reports on the use of protamine zinc insulin in diabetes. In a review by Wilder et al.[2] in 1940, it was pointed out that the most successful use of protamine zinc insulin is in patients with the milder forms of the disease. In contrast to this statement is the opinion of Tolstoi and Weber [3] who have treated patients with one large dose of protamine zinc insulin daily and disregarded the degree of glycosuria as long as there were no ketone bodies present in the urine. These two opinions probably represent the extreme views regarding the use of protamine zinc insulin.

We are reporting only patients whom we have observed constantly at regular intervals in the clinics for years. The diets of these individuals were not significantly changed at any time during these observations so that a fair idea of the effect of the protamine zinc insulin therapy, as compared with the effect of regular insulin therapy in a previous period, could be evaluated.

Procedure

These subjects were all patients attending the diabetic clinics of the Third (New York University) Medical Division of Bellevue Hospital or of the New York University College of Medicine Clinic. The patients visited the

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clinic at regular intervals which varied from two to four weeks. All the patients analyzed specimens of urine daily at home and brought such reports to the clinic. A urine analysis was done in the clinic at each visit. If hospitalization was necessary, the patients were hospitalized on the wards of the Third (N. Y. U.) Medical Division of Bellevue Hospital, and any therapy they received was under the direction of the same group of physicians during the period of this study.

In table 1 is given the sex, age and total period of observation of each of the 34 patients. The ages varied from 14 to 81; there were 14 males and 20

TABLE I

Case	Age	Sex	Onset of Diabetes	
			Year	*Age*
1. L.M.	46	female	1931	36
2. B.S.	55	female	1930	44
3. F.K.	42	male	1934	35
4. E.M.	45	male	1933	37
5. M.L.	39	female	1924	22
6. R.R.	14	female	1935	8
7. B.C.	38	female	1931	28
8. S.L.	28	female	1924	11
9. D.M.	17	female	1933	10
10. F.K.	42	male	1928	29
11. J.G.	21	male	1933	13
12. S.C.	36	male	1934	19
13. N.J.	38	male	1929	27
14. S.R.	75	male	1920	54
15. V.K.	21	male	1928	8
16. H.S.	81	female	1923	63
17. M.F.	51	female	1928	38
18. J.K.	28	male	1939	26
19. S.P.	16	female	1936	11½
20. P.M.	18	female	1939	16
21. E.N.	31	male	1938	28
22. E.P.	45	male	1931	35
23. S.L.	24	female	1935	17
24. M.C.	41	female	1933	32
25. M.S.	75	male	1919	53
26. M.A.	19	female	1937	15
27. E.R.	25	female	1935	19
28. A.A.	16	female	1935	10
29. V.R.	23	female	1936	18
30. A.E.	62	female	1938	59
31. G.G.	22	female	1930	11
32. J.H.	34	female	1939	32
33. S.P.	31	male	1939	29
34. N.D.	48	male	1932	39

females. The majority of the patients had had diabetes for about nine years and all but two of them were severe diabetics.

In table 2 the data on these patients, during the periods on regular insulin and during the periods on protamine zinc insulin, are given.

We are not of the opinion that it is absolutely imperative completely to control glycosuria in patients with diabetes, but neither does it seem to us that it is wise to allow unrestricted glycosuria which usually is sooner or later at-

TABLE II

Case	Regular Insulin						Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Total No. Units	Total No. Doses	Duration of Treatment in Months	Diet			Total No. Units	Total No. Doses	Duration of Protamine in Months	Total No. Units	Total No. Doses	
	C	P	F				C	P	F						
1 L. M.	200	70	85	145	4	62	200	70	85	125	2	17	40	2	Diabetes uncontrolled on protamine insulin 125 u. plus 40 regular insulin. Returned to regular insulin 50–20–50–30. Diabetes fairly well controlled. Weight unchanged.
2 B. S.	250	70	85	80	4	49	180	65	85	40	1	56	0	0	Diabetes difficult to control with regular insulin 80 u. in four doses. Diet cut from C250, P70, F85 to C180, P65, F85 and given protamine insulin 40–0–0. Patient has done well.
3 F. K.	250	70	85	85	4	5	250	70	85	35	1	48	30	2	Diabetes fairly well controlled. Less hypoglycemic reactions with protamine. Weight constant. General condition unchanged.
4 E. M.	200	75	85	60	4	5	200	65	85	20	1	56	60	2	Insulin now given twice daily but requires three injections, two regular and one protamine. Diabetes not controlled any better than on regular insulin. Weight increase 10 pounds. Mild glycosuria.
5 M. L.	200 300	75 75	85 85	85 55	4 2	45	300	75	85	40	1	53	35	1	Control of diabetes good for four years. The patient gained 10 pounds; general condition improved. The patient then began to experience shocks alternating with glycosuria. The protamine was reduced finally to 15 u., the time of administration changed to noon. Finally the protamine was discontinued and the patient was given 55 u. of regular insulin daily in two doses, and on this she was well controlled.
6 R. R.	250	75	85	45 70	3 2	15	320	75	95	25	1	9	15	2	Patient on protamine plus regular insulin for nine mos. Uncontrolled with numerous severe insulin shocks. Returned to regular insulin in three doses (80 u.), no shocks. Gained 31 pounds in 26 mos. Protamine no advantage.

TABLE II (*Continued*)

TABLE II (*Continued*)

Case	Regular Insulin						Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Total No. Units	Total No. Doses	Duration of Treatment in Months	Diet			Total No. Units	Total No. Doses	Duration of Protamine in Months	Total No. Units	Total No. Doses	
	C	P	F				C	P	F						
7 B. C.	200	75	85	50	3	37	250	75	85	35	1	51	15	1	Controlled on regular insulin but controlled as well on protamine and number of doses decreased to one a day. Gain of five pounds in three years (not overweight).
8 S. L.	200	65	85	75	4	36	200	75	85	30	1	10	20	2	Patient not controlled on protamine. Changed to regular insulin 15–8–10–5. Diet C–180–65–120. At present general condition not good. Pt. does not care for self properly. Glycosuria and insulin shocks, minimal. Husband has severe pulmonary tuberculosis which the patient has now developed.
9 D. M.	300	75	85	60	3	28	300	75	85	30	2	16	40	2	Patient uncontrolled on protamine plus regular insulin. Was changed to regular insulin 35–0–25 with diet C250 P75 F85, and is now improved.
10 F. K.	250	75	85	50	3	45	250	75	85	50	1	56	10	1	Patient improved on protamine. Has pernicious anemia, weight unchanged.
11 J. G.	350	75	85	100	4	31	350	75	85	40	2	62	20	2	Well controlled. Improved. Gained weight.
12 S. C.	300	75	85	110 115	4 4	36 36	380	70	95	90 40	2 1	21	40 75	2 3	Poorly controlled on protamine which was discontinued after 21 mos. Fairly well controlled on regular alone for 36 mos. Began again on one dose of protamine and three of regular.
13 N. J.	200	65	85	65	4	72	200	65	85	53 20	2 1	6 44	0 45	0 2	Patient experienced more insulin shocks on protamine than on regular. His diabetes was somewhat difficult to control as it was complicated by numerous rectal infections. After six mos. protamine was discontinued for about six mos. and then started again in combination with regular insulin. On this combination he is fairly well controlled.

TABLE II (*Continued*)

Case	Regular Insulin						Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Total No. Units	Total No. Doses	Duration of Treatment in Months	Diet			Total No. Units	Total No. Doses	Duration of Protamine in Months	Total No. Units	Total No. Doses	
	C	P	F				C	P	F						
14 S. R.	250	65	85	65	4	48	300	65	85	30	1	2	20	1	Patient in hospital for two mos.; could not control diabetes. Frequent and severe shocks. Returned to regular insulin with control of diabetes, 20–0–20–5.
15 V. K.	250	65	85	85	4	53	250	65	85	70	2	1	20	1	Had several admissions to hospital for ketosis. Impaired liver function with hepatomegaly. Protamine discontinued. Controlled on regular insulin 35–0–25.
16 H. S.	150	65	85	10	1	72	150	65	85	10 25	1 1	19 11	15 0	1 0	Patient was controlled on regular insulin, but because she was unable to take insulin herself she was switched to protamine which could be given once daily by a nurse. Controlled on 25 u. protamine alone now.
17 M. F.	150	65	85	32	2	36	150	65	85	40	1	25	5	1	Diabetes discovered in 1931. Remained untreated until 1936. Weight unchanged on regular or protamine insulin. Diabetes controlled equally as well. Takes insulin only once daily.
18 J. K.	250	65	85	80	2–3	10	250	65	85	20	1	2	15	1	Patient was started on 20–0–0 protamine and 15–0–0 regular, but was not controlled and developed persistent and increasing acetone. Changed to regular insulin 40–0–40. Control moderate.
19 S. P.	250	90	75	50	2	12	300	90	75	40	1	9	10	1	Patient came to clinic with 40–0–0 protamine and 0–0–10 regular. Glycosuria uncontrolled; insulin rearranged to 40–0–25 protamine. Gained 10 pounds. Not entirely controlled. Returned to regular insulin alone, two doses daily. Well controlled.

Case	Regular Insulin						Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Total No. Units	Total No. Doses	Duration of Treatment in Months	Diet			Total No. Units	Total No. Doses	Duration of Protamine in Months	Total No. Units	Total No. Doses	
	C	P	F				C	P	F						
20 P. M.				Never on regular alone			250	70	85	20	1	20	20	1	Patient started on protamine 15–0–0 upon discovery of diabetes. Lost weight, increasing glycosuria. Insulin raised to protamine 20–0–0, regular 20–0–0. Finally controlled on regular and protamine.
21 E. N.				Never on regular alone			350	70	85	30	1	27	50	2	Patient did not adhere to diet. At first controlled on protamine alone. Now requires protamine and regular.
22 E. P.	175	75	85	45	2	72	175	75	85	50	1	20	0	0	Patient was controlled on regular insulin 25–0–20, but changed to protamine 50–0–0 and continues well controlled.
23 S.L	200	75	85	45 45	2 3	22 12	230	75	85	15	1	18	15	1	Not well controlled on regular insulin. Changed to reg. 15–0–0, protamine 15–0–0, and is moderately controlled. Patient not very coöperative. Returned in March 1940 to regular alone. Was pregnant and delivered a normal child during the past year.
24 M. C.	180	75	85	70	3	24	150	65	85	30	1	31	15	1	Patient better controlled on protamine insulin 30–0–0 and regular insulin 15–0–0 than on regular 30–10–30.
25 M. S.	150	65	85	50	3	2	150	65	85	40	1	13	0	0	Patient improved on protamine. Diabetes fairly well controlled. Fewer injections.
26 M. A.	300	65	85	55–70	3	24	300	65	85	40 25	1 2	22 7	0 20	0 2	Patient started on protamine and kept on it for ten months. Became difficult to control. Changed to regular insulin and continued on it for 24 months but was inadequately controlled with the development of her menses. Began again on protamine as a supplement to regular insulin and carried on this seven months. Controlled fair on this combination.
27 E. R.	200	65	85	100	4	7	200	65	85	25	1	18	65	2	Patient always difficult to control. Started on regular insulin and fairly well controlled. Because of frequent injections changed to protamine and regular. Patient fairly well controlled.

TABLE II (*Continued*)

Case	Regular Insulin						Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Total No. Units	Total No. Doses	Duration of Treatment in Months	Diet			Total No. Units	Total No. Doses	Duration of Protamine in Months	Total No. Units	Total No. Doses	
	C	P	F				C	P	F						
28 A. A.	230	85	55	95	4	3	180	65	85	80 30	2 2	19 2	40 0	1 0	Patient fairly well controlled on four doses of regular insulin. Changed to protamine and regular in two doses. Fairly well controlled. In Jan. 1941 stopped regular insulin. Now on two doses of protamine.
29 V. R.	175	75	85	75	4	13	175	75	85	8	1	36	45	2	Patient on four doses of regular insulin fairly well controlled. Placed on two doses with one dose protamine. Well controlled. B.M.R. +36.
30 A. E.					None		150	75	85	15	1	12	0	0	This patient was never on regular insulin. She was at first given protamine insulin alone. This was cut to 10 u. and she was well controlled. Finally insulin was omitted altogether and she continued to be sugar-free. This is a very mild diabetic and probably would have done equally well on regular insulin.
31 G. G.	150	65	70	90	3	37				40	2	60	40	2	Patient controlled first on regular insulin. Then transferred to regular and protamine, and has been well controlled on dose stated.
32 J. H.	280	90	90	10	1	16	200	70	75	10	1	7	0	0	This patient developed diabetes during her first pregnancy. She was never difficult to control and she was carried on protamine insulin for seven mos. but noted a tendency to insulin reaction. She was changed to regular insulin, the same dose, had no reactions and said she felt better. The dose of insulin is now reduced to 8 units of regular.
33 S. P.	275	80	95	60	2	2	314	80	95	25	1	22	20	2	When this patient was regulated on regular insulin he was changed to regular and protamine. For nine mos. he required only one dose of regular, but since then has required two doses to supplement the one dose of protamine.
34 M. D.	200	65	90	25	2	70				15	1	34	25	2	This patient is fairly well controlled on this regimen. He was transferred to protamine because two doses of regular insulin were not enough to control his diabetes.

tended by loss of weight and a tendency to ketosis. In this group our effort was to keep each patient moderately sugar-free, to maintain his body weight, and to provide him with a diet that was adequate for his daily needs. Insulin was given in sufficient doses to accomplish these results.

In discussing the effects of protamine zinc and regular insulin on this group of patients, the criteria that we have used to indicate improvement on protamine zinc insulin are: (1) a smaller number of injections daily; (2) improvement in the general clinical condition of the patient, such as gain in weight; (3) a decrease in the number of units of insulin required daily.

Analysis of the cases reported in table 2 shows that nine of them (1, 6, 8, 9, 12, 14, 15, 18, and 19) did not improve with protamine zinc insulin, and in fact did poorly on it so that they were returned to regular insulin alone. Six of the nine cases who did not do well on protamine zinc insulin were kept on this insulin for periods varying from 9 to 21 months. The other three were given a trial in the hospital for periods of one or two months. The difficulty in most of these cases was severe insulin shock. This occurred regardless of the time the protamine zinc insulin was given and was severe enough to cause unconsciousness. The other most annoying symptom was intense headache.

The course of the diabetes in these nine cases since their return to regular insulin has been observed for periods varying from 10 to 62 months. Two of these patients (cases 1 and 18) are not well controlled on regular insulin. These patients are not coöperative, and it is impossible properly to evaluate the effect of either type of insulin. One patient (case 9) has developed tuberculosis and this has somewhat influenced her insulin requirement, but while under our observation she was well controlled on regular insulin. The other six patients have been controlled on regular insulin. In case 12 numerous adjustments of the dose of insulin have been required as the patient is going through the period of adolescence, and under these circumstances it is quite usual for the insulin requirement to vary somewhat. Four patients (cases 4, 13, 23, and 32) did no better on protamine zinc insulin than they had done on regular insulin. One patient (case 5) did well on protamine zinc insulin alone for almost four years but then became difficult to control and was finally returned to regular insulin. This disposes of 14 of the cases studied.

The other 20 patients may be considered to have done better on a combination of protamine zinc insulin and regular insulin than on regular insulin alone and among these some did much better than others. Examples of those who did really well on protamine zinc insulin were: Case 2 in which four doses of regular insulin were required daily; for the past 56 months one dose of protamine zinc insulin has sufficed. Case 7, which showed good control by regular insulin, but on protamine zinc and regular insulin the patient needs to take insulin only once daily in two injections. Case 10, in which pernicious anemia was a complication. The patient required regular

insulin three times a day, but now takes one dose of regular and one of protamine zinc insulin and is well controlled. Case 11, in which the requirement was four doses of regular insulin daily. The patient is now controlled on protamine zinc and regular insulin given twice a day. Case 16, in which control is now maintained by protamine zinc insulin alone. Cases 20 and 21, patients who were never treated with regular insulin alone but who have

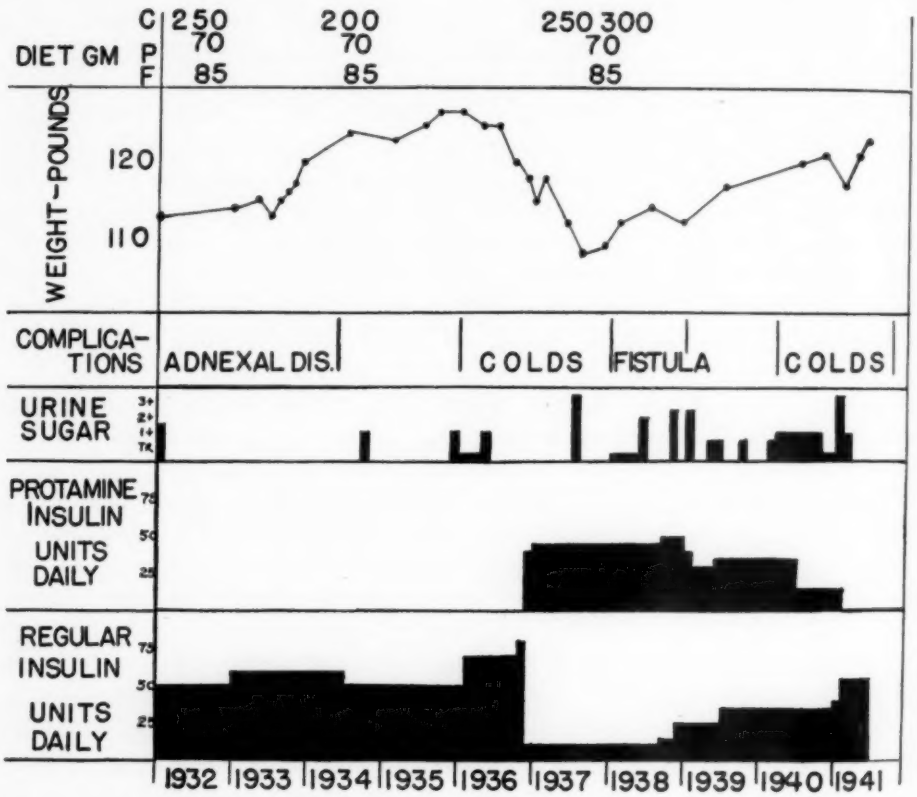

CHART 1. Graphic representation of the course of diabetes mellitus in Case 5 while being treated with regular insulin and while under protamine zinc insulin therapy.

done well on a combination of protamine zinc and regular insulin. Case 22, in which two doses of regular insulin were formerly required and the diabetes now is controlled on one dose of protamine zinc insulin. Case 24, in which the patient is better controlled on the combination of protamine zinc and regular insulin than she was on regular insulin alone. Cases 25 and 28 which demonstrate control by fewer injections of protamine zinc insulin alone. Case 30, satisfactory continued treatment by protamine zinc insulin alone. Case 31, improved control by protamine zinc and regular insulin as compared with regular insulin alone. Case 33 in which the patient has done well on protamine zinc and regular insulin.

Of these 20 cases six have been well controlled on protamine zinc insulin alone. The rest have required combinations of protamine zinc and regular insulin.

Discussion

From this group of 34 patients, most of whom have been under observation for an average of four and one-half years, one gets a fair idea of the course of diabetes as influenced by regular and protamine zinc insulin. The cases that showed the most striking improvement on protamine zinc insulin are those that can be handled with one dose of the latter daily. This obviously is much more convenient for the patient. In the majority of the cases, however, it is apparent that protamine zinc insulin alone is not sufficient to control the glycosuria, and it becomes necessary to use a combination of protamine zinc and regular insulin. In some of these cases this combination is an improvement on the use of regular insulin alone; in others the control of the diabetes is no better on the combination than on the regular insulin alone. In the latter event one wonders whether there is any point in using protamine zinc insulin.

Some cases apparently do not respond well to the use of protamine zinc insulin. These patients are almost invariably severe diabetics and often may not be well controlled on regular insulin, due to a lack of coöperation on the part of the patient.

In using protamine zinc insulin in the treatment of diabetes some patients will respond better than others, and it is interesting to note that some patients do very well on protamine zinc insulin for a period of years and then for some reason or other seem to require more regular insulin, or protamine zinc insulin has to be abandoned altogether. It is possible that this is due to lack of absorption of the protamine zinc insulin. Many patients have complained that they have found it increasingly difficult to find a place to inject protamine zinc insulin after this insulin has been used for years.

As a result of our observations over the past six years it is our policy to try patients on a combination of protamine zinc and regular insulin, arranged in such a way that the patient will not have to take insulin more than twice daily. Our effort is to reduce the number of doses to a minimum which will control the patient's diabetes sufficiently well so that he does not lose weight and is capable of doing his work. In cases where patients have required frequent doses of regular insulin we have endeavored to use the combination of protamine zinc and regular insulin and, as the results show in these 34 cases, this has been possible in about 60 per cent of the cases. We have learned also that in using protamine zinc insulin one must adjust it to the needs of the particular patient. It is our impression that not more than 40 units should be given in one dose. It seems as if larger doses than this are not correspondingly effective. One of the most effective methods of using protamine zinc insulin is in patients who have previously required a

dose of regular insulin late at night in order to remain sugar-free through the night. In such cases, as pointed out also by Martin et al.,[4] by giving a dose of protamine zinc insulin at supper time the glycosuria which occurs at night, and often is the cause of nocturia, is avoided.

Several of the patients in this study were hospitalized at times because of some intercurrent infection. During the period of infection it was observed that the patients did better on regular insulin alone than on combinations of regular and protamine zinc insulin. Two outstanding examples were cases 2 and 13. In case 2 the patient suffered from chronic gall-bladder disease and during acute attacks which required hospitalization it was found necessary to treat her with regular insulin every two hours to control the glycosuria and the ketosis. In case 13 recurrent rectal abscesses raised the patient's insulin requirement and it was necessary to give him regular insulin every three hours during the acute period to prevent ketosis and control the glycosuria. It is our feeling that during the period of an acute infection it is wiser to use regular insulin alone as it is easier to control the glycosuria, and as the infection subsides there is no danger of insulin shock as from an overdose of protamine zinc insulin.

Some of the divergence of opinion as to the efficacy of protamine zinc insulin in the treatment of diabetes possibly results from the fact that the patients have not been under observation for a sufficient period of time, and often are not seen by the same observer during varying periods of the disease. The fact that the diabetic patient is well controlled on protamine zinc insulin for some time and then goes through a period in which he does not respond so well may be due to several factors. First among these may be poor absorption of the protamine zinc insulin. Second may be the occurrence of intercurrent infections which always tend to increase the severity of the diabetes. Third is the possibility that the patient may not be adhering to his diet. It has seemed to us that the best policy is to adjust the insulin, whether it is protamine zinc or regular insulin, to the patient's needs. It does not seem to us that one can assume too dogmatic a point of view, as it is obvious that when the diabetic patient is observed for a sufficiently long period there will be times when his insulin requirement will change, and at these times it also seems that the type of insulin best suited to his needs may change. On the whole, the most efficient method of using protamine zinc insulin is as a supplement to regular insulin. Its more prolonged action makes it possible in some cases to omit the midday and night injections of regular insulin, and this action also tends to stabilize the patient's carbohydrate metabolism.

SUMMARY

A group of 34 diabetic patients observed on both regular and protamine zinc insulin is reported. The average period of observation was four and one-half years. Of these patients, six were well controlled on protamine zinc

insulin alone; 14 did better on combinations of protamine zinc and regular insulin than on regular insulin alone. Treatment with protamine zinc insulin was ineffective with nine of the patients and they were returned to regular insulin alone, on which they were controlled. Four patients did as well on regular insulin alone as they did on combinations of protamine zinc and regular insulin. One patient who had been treated with protamine zinc insulin alone for almost four years became impossible to control and it was necessary to return her to regular insulin.

It is felt that a combination of protamine zinc and regular insulin is an effective way of controlling glycosuria in the diabetic patient, but it is important to realize that such procedure may have to be altered during periods of acute infection.

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CONVULSIONS IN PAGET'S DISEASE; ELECTRO-ENCEPHALOGRAPHIC OBSERVATIONS *

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Recent electroencephalographic studies have thrown new light on the question of hereditary factors in epilepsy. Evidence has been presented which not only substantiates the long accepted view as to the importance of heredity in idiopathic epilepsy but also tends to break down the distinction which until now has divided convulsive states into idiopathic and symptomatic varieties. Strauss, Rahm, and Barrera,[1] and Lowenbach [2] have demonstrated an increased occurrence of cerebral dysrhythmia among supposedly normal relatives of epileptics. Lennox, Gibbs and Gibbs [3] obtained abnormal tracings in 60 per cent of the relatives of 94 patients with convulsions and cerebral dysrhythmia, and found that dysrhythmia occurred as frequently among the relatives of patients with symptomatic epilepsy as among relatives with the idiopathic variety. In a control group of 100 persons who had no near relatives with epilepsy, 10 per cent had abnormal records. These workers have concluded that cerebral dysrhythmia represents visible evidence of a constitutional predisposition to epilepsy or some allied disorder, and that the dysrhythmia of epilepsy is inheritable.

Recently two patients with convulsive seizures beginning late in life came under our observation. Both were found to have osteitis deformans with involvement of the skull. Careful study failed to reveal in either case any other associated disease which could account for the seizures. The occurrence of convulsions in the son of one of the patients led us to investigate the electroencephalographic findings in these patients, in five other cases of Paget's disease in the hospital, and in all available near relatives.

Interpretation of Electroencephalographic Records

The electroencephalographic abnormalities which have been found in cases of epilepsy may be considered in regard to: first, the spontaneous tracing, and second, the effects of hyperventilation. Gibbs and Gibbs [4] feel that the occurrence of alternating slow wave and spike activity is diagnostic of petit mal and that there is a definite difference between petit and grand mal tracings, the latter being marked by the occurrence of abnormally slow or fast waves in interseizure periods. The "crescendo burst of fast waves" which they find during actual grand mal seizures are rare in their interseizure

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records. They consider findings during hyperventilation as of limited value in the electroencephalographic diagnosis of epilepsy.

In this laboratory,[5] experience with a large number of clinically diagnosed epileptics has shown that the occurrence of bursts of high amplitude slow waves without preceding gradual slowing, usually of a 3 per second frequency and with or without interspersed spikes, is also a characteristic feature of the convulsive state whether of the petit or grand mal type. It is further felt that on the basis of comparison with many normal controls, the appearance of such waves during or after measured periods of deep over-ventilation (180 seconds) is of definite diagnostic significance in epilepsy.

In the records discussed in this paper, both the spontaneous and hyperventilation portions were carefully examined for any of the above mentioned abnormalities.

Case Reports

Case 1. S. G. a 45-year-old white man, was admitted to Montefiore Hospital on July 31, 1940, complaining of episodes of unconsciousness of six years' duration. His health had been excellent up to the onset of his present illness. He was married and had one child, a five year old son, who on two occasions in the past two years had been observed to have attacks of generalized twitchings with unconsciousness. The boy was receiving daily phenobarbital medication. The patient's wife had never had a convulsion and there was no other history of epilepsy, migraine, chorea, or allied disorders in the family. There was no background of alcoholism. Three months before his first convulsion the patient was in a brawl and was beaten about the nose and eyes. His face was discolored but there was no loss of consciousness and no confusion. There were no headaches or dizziness following this episode and no apparent disability. The first seizure consisted of a two minute period of unconsciousness. Since that time, he has had repeated attacks occurring at intervals of 30 to 90 days, with their frequency increasing during the past two years. There is no aura preceding the seizure, which may occur either during the day or night. In the attacks which have been observed recently the body becomes rigidly arched and the face twitches. At times there is biting of the tongue and drooling of saliva. Neither generalized nor local clonic movements have been observed.

Physical Examination. The patient was a short, rather plethoric white man who did not appear ill. His head was somewhat enlarged but not unduly so. His hat size had increased from 7⅛ to 7¼ in the past year. General examination revealed no abnormalities and the neurological status was completely negative. Carotid sinus pressure had no perceptible effect.

Laboratory Data. A roentgenogram of the skull revealed numerous circular areas of bone condensation in the fronto-parietal region. The appearance was typical of osteitis deformans. In roentgenograms of the pelvis there was marked bone condensation in the right sacro-iliac synchondrosis also considered to be due to Paget's disease. On August 11, 1940, an air encephalogram was made and revealed only slight dilatation of the lateral and third ventricles. Blood phosphatase level was 31 Bodansky units (normal level 4 to 6 units). Blood calcium and phosphorus were within normal limits. The glucose tolerance test was normal. There were no abnormalities of the spinal fluid.

Electroencephalography. (Figure 1.) In the spontaneous record the predominant alpha activity was of 10 per second frequency, the beta of 18–24 per second. In addition, there were low voltage slow waves and fast spike activity appearing in

bursts. During four hyperventilations, the patient developed outbursts of high amplitude, three per second waves in all leads. These continued to appear for some time after cessation of over-ventilation.

Case 2. N. L., a 63-year-old white salesman, was admitted to Montefiore Hospital on February 16, 1941 because of fainting spells of six months' duration. His birth and early life were uneventful except for constant headaches between the ages

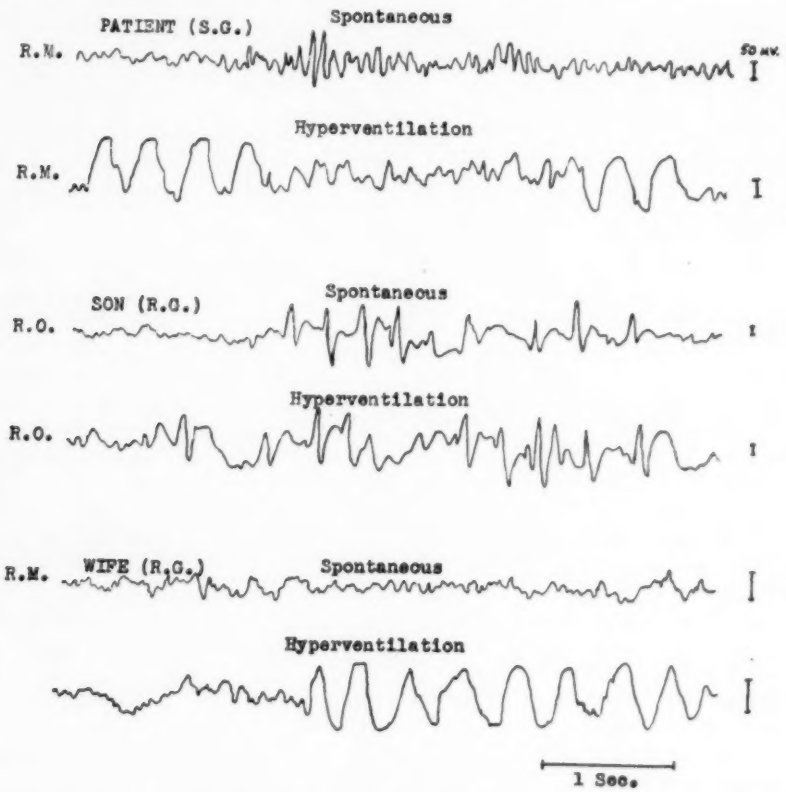

FIG. 1. Tracings from patient, S. G., son, and wife. The spontaneous record of the patient shows an abrupt transition from normal to high amplitude, spike activity. The hyperventilation record shows two outbursts of high amplitude, three per second waves with suggestive spike formation in the first. Typical wave and spike configurations are shown in both the spontaneous and hyperventilation records of the patient's son who has clinical epilepsy. The spontaneous record of the patient's wife shows slight disorganization. In the hyperventilation record is shown a prolonged burst of high amplitude, three per second waves.

of 10 and 14 which necessitated his leaving school. At 14, the headaches ceased spontaneously and did not recur until the present illness. Beginning at the age of 30, the patient noticed a gradual and progressive increase in the size of his head. At the age of 30 his hat size was 7½; at present a size 8¾ is too small for his head. The changes have been more pronounced during the past year. For the past 20 years, there has been a gradual diminution in hearing in the left ear. Four months before admission he developed progressive loss of hearing in the right ear so that at present he is almost totally deaf. After 1932, he noticed a decrease in visual acuity. His present complaints date back to six months before admission when he developed

attacks of dizziness and fainting spells occurring about once every three to four weeks. Each attack of syncope came on during the day while the patient was walking on the street and was preceded by several minutes of dizziness during which surrounding objects seemed to move about him. He would then suddenly lapse into unconsciousness for a period of two to three minutes. Upon awakening, there was complete amnesia for the event. At times, the entire attack consisted only of the prodromal vertigo. Coincident with the fainting spells the patient developed "shooting pains" in the temples which radiated posteriorly to the occiput. Five months before admission, he noted the onset of dull, aching pains in his knees, hips, elbows, thighs, and back. In addition to the fainting spells which have been described, the patient had one generalized convulsive seizure in his home on Thanksgiving Day, 1940. There was no vertigo preceding this attack. According to his wife, who witnessed the seizure, there were involuntary clonic movements involving the face and all extremities. There was no frothing at the mouth and no incontinence. He was unconscious for a period of two to three minutes.

Physical Examination. The patient was a tall, well-developed white man in no acute distress. The head was markedly enlarged and presented prominent parietal bosses. The circumference was 66 centimeters. The heart was slightly enlarged to the left. Blood pressure was 118 systolic and 80 diastolic. The pulse rate was 68 per minute and auricular fibrillation was present. There was a systolic apical murmur. The peripheral vessels were moderately sclerotic. Carotid sinus stimulation produced no demonstrable effect.

Neurological Examination. The tendon reflexes in the upper extremities were hypoactive. There was a defective plantar response on the left but no pathological reflexes. Smell was impaired bilaterally, right more than the left. There was a right divergent strabismus with crossed diplopia on looking to the right. Vision in the right eye was reduced to 1/50; the right visual field showed an irregular constriction. The right optic nerve head appeared lemon-yellow in color. There was evidence of retinal arteriosclerosis. Hearing was markedly impaired bilaterally with almost complete deafness on the left. There was diminution of both bone and air conduction. The audiometer test revealed marked impairment of perception of the higher notes indicating bilateral nerve deafness.

Laboratory Data. The urine and blood count were normal. Blood phosphatase level was 55 Bodansky units. A spinal tap revealed an initial pressure of 153 mm. of fluid with normal manometric alterations on test. The total protein was 51 mg. per cent. Blood and spinal fluid serology were negative. An electrocardiogram showed left axis deviation and auricular fibrillation. Caloric testing showed complete absence of response on the right and slight response on the left. Roentgenograms of the skull, spine, and pelvis revealed bony changes typical of Paget's disease.

Electroencephalography. (Figure 2.) In the spontaneous record there was very little alpha activity and this was of 12 per second frequency. There was a large amount of beta activity. In some places, waves of increased amplitude suggestive of spikes, and irregular slow waves of varying amplitude and frequency appeared. Both during and after hyperventilation, there were outbursts in all leads of high amplitude three per second waves.

COMMENT

A review of the literature reveals that convulsions are not a common accompaniment of osteitis deformans. In his original description in 1876, Sir James Paget [6] expressed surprise that "the mind remains unaffected even when the skull is hugely thickened." Marie [7] describes a case exhibiting

fugues, epileptic attacks, and diabetes insipidus. In addition to having osseous disease this patient was a chronic alcoholic. Cahane and Cahane [8] report a case of epilepsy associated with Paget's disease occurring in a young woman. In a series of 34 cases of osteitis deformans with neuropsychiatric complications Kay, Simpson, and Riddoch [9] describe one with generalized convulsive seizures. Kasabach and Gutman,[10] writing on osteoporosis circumscripta, which they consider a variant of osteitis deformans, report out of 20 cases one in which generalized convulsions occurred. Grünthal [11] and Nonne [12] state that epileptic attacks occur in Paget's disease but give no examples in their own material. Many other reports on the neuropsychiatric complications of this disease (Wyllie,[13] Gregg,[14] Schwarz and Reback,[15] Moynan,[16] and Kaufman [17]), although describing cranial nerve involvement, cord compression, and mental changes, do not mention convulsions as a symptom. Gutman and Kasabach,[18] in an analysis of 116 cases, and Sugarbaker,[19] in 51 cases, do not report convulsions.

Since cranial osteitis deformans does not cause convulsions in a majority of cases, how then are we to explain the occurrence of seizures in some cases of this disease in which there is no other adequate explanation? The work of Lennox, Gibbs and Gibbs [3] suggests that epilepsy, both the "idiopathic" and the so-called "symptomatic" varieties, rarely occurs without an inherited predisposition. In both our cases convulsive seizures began long past the usual age of onset of idiopathic epilepsy; and in neither of them is there any evidence of focal brain disease. Electroencephalographic tracings reveal in both the diffuse cerebral dysrhythmia seen in epilepsy and allied conditions. It may be that the postulated inherited predisposition in these patients is of such low intensity that under ordinary circumstances their lives might have been passed without clinical expression of their epileptic tendency. It required the intervention of a precipitating factor, in this case Paget's disease, to allow the convulsive explosion to break through.

In order to further investigate the validity of this hypothesis of hereditary predisposition, electroencephalographic tracings were obtained of the available near relatives of our two patients. The only child of S. G. (case 1) is of particular interest since he is known to have had two episodes of generalized twitchings with loss of consciousness. The record of this boy revealed frequent spontaneous outbursts in all leads of three per second waves and spike formations (figure 1). For the sake of completeness a record was obtained of the child's apparently normal mother, the wife of S. G. Although the spontaneous record was within normal limits, both during and after hyperventilation there were outbursts of high amplitude, three per second waves (figure 1). The three members of this family thus provide a cogent example of the different ways in which hereditary predisposition and precipitating factors may interact. In the case of S. G. an inherited predisposition plus an exogenous factor resulted in clinical epilepsy. His wife, with a probable mild predisposition and no exciting cause, escaped overt

manifestations. The child of this union, the victim of a double inheritance, developed frank epilepsy early in life.

The two children of N. L. (case 2), neither exhibiting clinical evidence of epilepsy, were also subjected to electroencephalography (figure 2). The record of the daughter, aged 35, showed some spontaneous slow waves and an alternating fast and slow rhythm. During hyperventilation there ap-

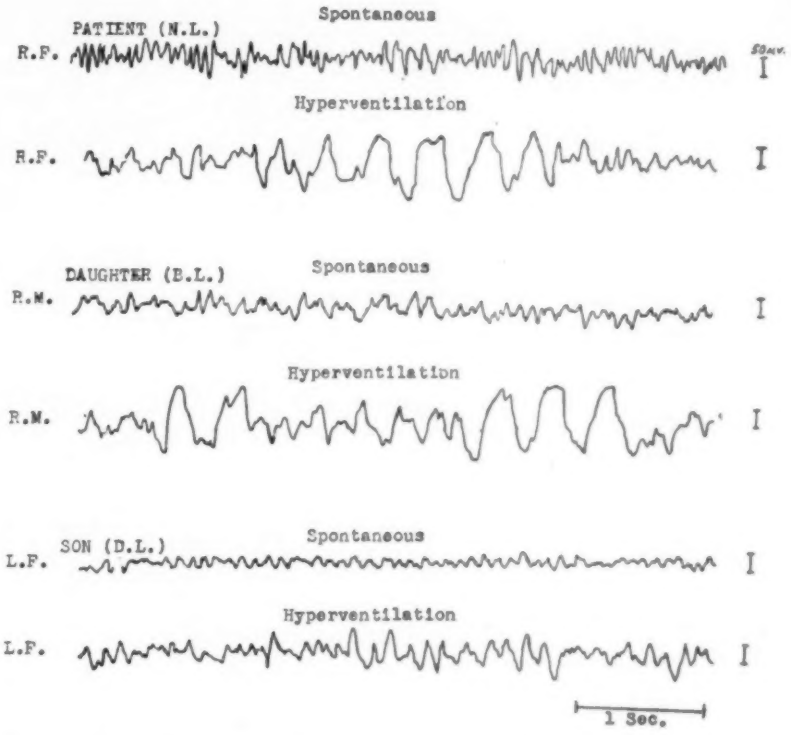

FIG. 2. Tracings from patient, N. L., daughter, and son. The patient's spontaneous record shows disorganization with waves of increased amplitude suggestive of spikes and some irregular, slow activity. During hyperventilation, an outburst of high amplitude, slow waves is shown. The spontaneous record of the daughter shows abnormal slow activity. In the hyperventilation record an outburst of high amplitude, slow waves is illustrated. Such outbursts, however, were relatively infrequent during the over-ventilation period. The spontaneous record of the son is normal. The maximum change occurring after 180 seconds of hyperventilation is shown.

peared a few bursts of high voltage three per second waves in all leads. The tracing of the son, aged 31, was within normal limits. In this family, the daughter's borderline record may or may not be evidence of a transmissible factor.

To eliminate the possibility that cranial osteitis deformans per se may produce a diffuse cerebral dysrhythmia, electroencephalographic records were obtained on five other cases of Paget's disease present in the hospital for various non-neurological complaints including cardiac decompensation, frac-

ture of the femur, and one with syphilis and optic neuritis. The ages of four of the five ranged from 58 to 84; the fifth was 40 years old. In none was there a personal or family history of convulsions. The tracings displayed such abnormalities as slowing of alpha activity, and inconstant slow waves of four to seven per second frequency not appearing in all leads. The patient with optic atrophy of the right eye showed alpha activity of increased amplitude on the right side, and numerous slow waves of six to seven per second frequency originating from the right occipital region. Neither

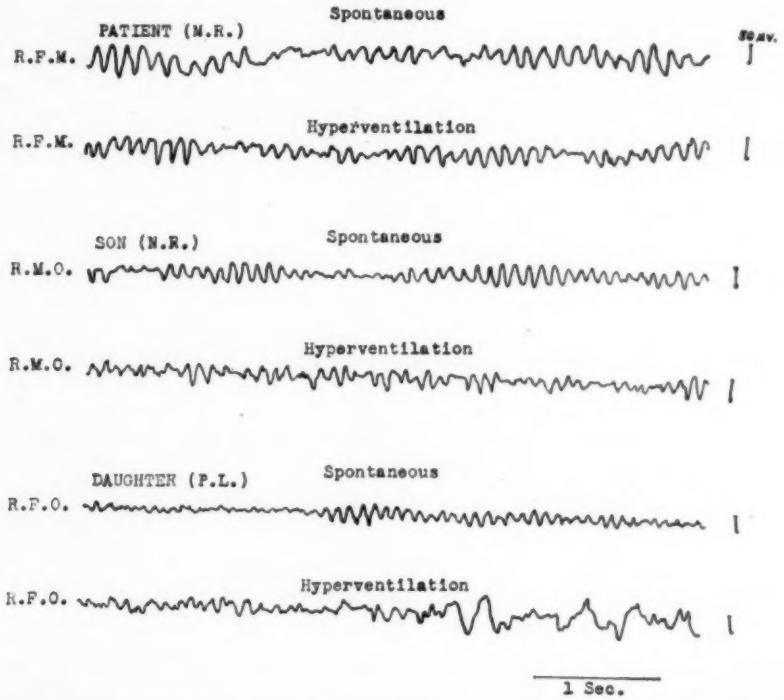

FIG. 3. Tracings from one of the five cases of Paget's disease without convulsions, and from his son and daughter. All spontaneous records are normal. In the records of the patient and his son there is very little change during hyperventilation; in the daughter's record, only the gradual development of irregular, slow activity is shown.

spontaneously nor during hyperventilation did any of these tracings remotely resemble a diffuse cerebral dysrhythmia. Hyperventilation, in contrast to the first group of cases, while causing some gradual slowing, failed to produce outbursts of three per second waves (figure 3). The records of four children of two of the patients in this latter group were obtained and all were within normal limits.

Although no final conclusions can be drawn from a series of this size, it is noteworthy that none of these five patients displayed electroencephalographic evidence of the cerebral dysrhythmia seen in epilepsy, and that normal records were obtained in four relatives of two of them. These findings,

along with the negative family histories of this group for convulsions, would indicate a lack of the transmissible factor which predisposes to epilepsy. This would suggest that a local factor in the absence of an hereditary tendency may be insufficient of itself to produce seizures. In line with the fact that statistical studies of Lennox, Gibbs, and Gibbs [3] have demonstrated that 10 per cent of the normal population exhibit cerebral dysrhythmia, it is of interest to note that of a group of 305 patients with delirium tremens Rosenbaum, Lewis, Piker, and Goldman [20] found an incidence of convulsions in 9 per cent. The close approximation of these two figures suggests that possibly the patients who experienced convulsions were those who were endowed with a predisposition to epilepsy and were thus unable to withstand an additional insult, in this case the cerebral effects of alcohol.

Just how the changes of Paget's disease can act as a precipitating cause in lowering the convulsive threshold of patients predisposed to epilepsy cannot be stated with certainty. Several possibilities suggest themselves. The most obvious of these would seem to be compression of the cortex by the thickened calvarium. The anatomical studies of Leri,[21] Marie and Leri,[22] Knaggs,[23] and Wyllie [13] all show that, although there is a decrease in the vertical diameter of the intracranial cavity, its actual capacity remains undiminished due to the compensatory increase of the antero-posterior and transverse diameters. However, in some cases of osteitis deformans which came to necropsy (Marie and Leri [22]) osseous protuberances from the inner table of the skull were observed. It is possible that in predisposed cases similar bony overgrowths might act as an epileptogenic agent by local compression of the cortex.

The association of generalized arteriosclerosis with osteitis deformans has often been commented upon and has been variously considered to be either the cause of the bone changes (Leri [24]) or an accompanying manifestation of the same underlying toxic or metabolic disorder (Knaggs [23]). Since convulsions are known to occur in some cases of cerebral arteriosclerosis, one might attribute their occurrence in Paget's disease to the vascular changes. The comparative rarity of seizures in this disease would again demand an explanation as to why they occur in some and are absent in the majority of cases. One cannot exclude the possibility that in predisposed cases cerebrovascular changes may be of sufficient severity to act as the precipitating agent. This may be equally true in cases of cerebral arteriosclerosis uncomplicated by Paget's disease.

If, on the other hand, Paget's disease is fundamentally a metabolic disorder (Gutman and Kasabach [18]), local changes in cerebral intra-cellular chemical processes (Putnam [25]) secondary to the disturbed metabolism could account for the lowered convulsive threshold and in constitutionally predisposed individuals give rise to clinical epilepsy.

Summary and Conclusions

1. Two cases of Paget's disease (osteitis deformans) with convulsions are presented.

2. Electroencephalographic findings in these patients, their available near relatives, and in five other cases of Paget's disease without convulsions are reviewed.

3. The question of a constitutional predisposition to epilepsy is discussed in the light of these electroencephalographic findings.

4. Evidence is offered to emphasize the relative rôles of hereditary and precipitating factors in the production of convulsive states.

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A THEORY EXPLAINING THE LOCAL MECHANISM FOR GASTRIC MOTOR AND SECRETORY CONTROL AND THE ALTERATION OF THESE FUNCTIONS IN UNCOMPLICATED DUODENAL ULCER *

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THE symptomatology of duodenal ulcer is due in large part to the disordered gastric physiology. It is also true that if an adequate explanation for the disordered physiology were available, therapy could possibly be directed into more physiological channels than is now the practice. The disordered gastric function in duodenal ulcer, as is well known, takes the form of both motor and secretory changes. In uncomplicated cases, the abnormal motor phenomena are hyperperistalsis, hypertonicity, and hypermotility. The secretory abnormality is hypersecretion. These abnormal gastric findings have long been recognized, but no suitable explanation for their existence has as yet been given.

The presence of hydrochloric acid in the duodenum, in man, affects the gastric motor function.[1] Especially striking are the effects produced by the addition of acid to the test meal in the achlorhydric subject. A water-barium meal, observed fluoroscopically in uncomplicated cases of gastric anacidity, shows a rapid gastric emptying, frequently in the absence of all peristalsis, and poor gastric tone. If for the water a hydrochloric acid solution of as little as 0.1 per cent concentration is substituted, gastric emptying is materially slowed, and instead, the almost continuous stream through the pylorus of the water-barium meal is replaced by an intermittency of gastric emptying resembling that in the normal individual.[1] The addition of acid to the water-barium meal produces gastric motor delay also in the normal acid stomach, but with the weak acid mixtures the change is less marked than in the anacid individual and becomes more marked only with stronger acid solutions.[1] When the weak hydrochloric acid solutions (less than 0.2 per cent) are slowly dripped into the duodenum a delay in gastric emptying is produced in all cases, although its intensity is influenced somewhat by the individual gastric acid response. These differences have already been fully discussed.[1] With more concentrated solutions (greater than 0.25 per cent), this difference in behavior disappears and the delay in gastric emptying in all groups is very

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With the technical assistance of Herman Siplet, A.B.

marked. The effects of such duodenal instillations have led us to believe that the *local* mechanism concerned in gastric emptying is controlled from the proximal duodenum and that the gastric hydrochloric acid is the intrinsic agent which when it arrives in the duodenum activates this mechanism. Furthermore, we have seen this mechanism operate in the human subject by prolonging pyloric closure. The intermittent emptying of the normal stomach may be visualized as follows: When gastric acid reaches the duodenum in concentration sufficient to activate the local mechanism, pyloric closure occurs until the neutralizing agents in the duodenum have reduced the acidity to a level which permits the pylorus to reopen. The stronger the acid concentration reaching the duodenum, the longer the periods of pyloric closure and the greater the prolongation of gastric emptying.

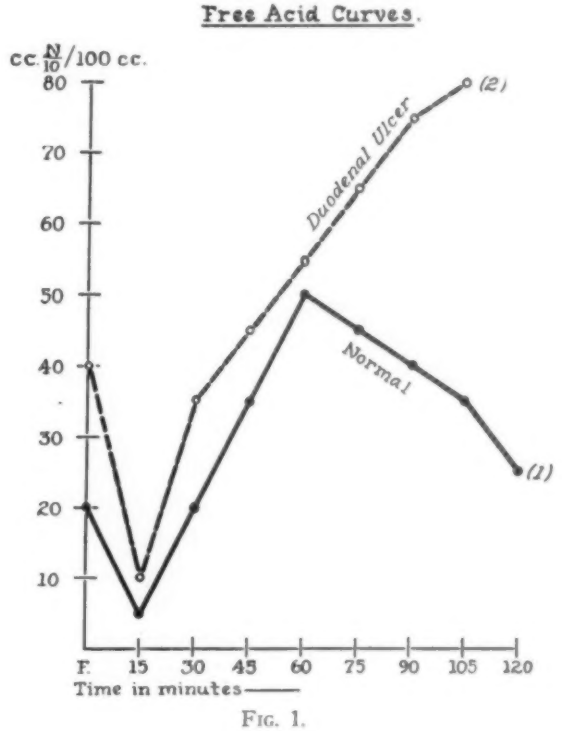

FIG. 1.

Figure 1, curve 1 represents the free acid curve usually obtained in the normal individual from the type of test meal we employed. Gastric emptying of a water-barium meal, if observed at short intervals, will be seen to follow closely in an inverse manner the pattern of this curve. This fluoroscopic observation will show that gastric evacuation is relatively active in the first 15 to 30 minutes after the ingestion of the water-barium meal. This corresponds to the period of gastric acid dilution by the meal. Gastric evacuation then slows materially—this corresponds to the period of increased

gastric acidity. (Ascending limb of the curve.) Evacuation is then again accelerated to correspond to the descending limb of the gastric acid curve. (Water is quite capable of stimulating gastric secretion.—Ivy.)

In addition to the influence upon pyloric action, we have seen, too, striking effects of the acid upon gastric peristalsis and gastric tonus. Pyloric closure, caused by acid in the duodenum, is rapidly followed by a diminution of gastric peristalsis, which shows renewed activity as the acidity in the duodenum is reduced. Although a similar relationship between pyloric tonus and gastric tonus is more difficult to demonstrate in the human stomach, by our method of experimentation, we believe such a relationship exists.

In brief, then, gastric hydrochloric acid reaching the normal duodenum in concentration capable of stimulating the duodenal mechanism causes pyloric closure and decreases gastric peristalsis and tonus.

Duodenal ulcer is usually situated in the most active area of the above described mechanism, i.e., the cap. This location of ulcer coupled with the associated duodenitis of the adjacent duodenum results in partial destruction of the mechanism or a rise in the threshold of response. The normal intrinsic brake upon gastric emptying is reduced and the natural result is rapid gastric emptying with increased gastric peristalsis and tonus, three motor phenomena well known in uncomplicated duodenal ulcer.

We have demonstrated [2] that the duodenal instillation in man of many substances capable of stimulating the duodenal mucosa chemically or physically will activate a mechanism that depresses gastric secretion. From results obtained with weak solutions of hydrochloric acid we are convinced that this mechanism can explain the drop in acidity in the normal fractional gastric analysis after the peak of the gastric acid curve has been reached.[2] In the disturbance of this mechanism in duodenal ulcer lies, we believe, the explanation for the secretory changes so frequently seen in this disease. Although we realize that no gastric secretory curve is pathognomonic of any disease, we believe that the hypersecretory extra-gastric curve occurs with such regularity in duodenal ulcer that it comes closest to representing a characteristic response (figure 1, curve 2).

Our previous studies [3] indicate that the gastric hydrochloric acid acts as a self-regulator of its own secretion when it reaches the normal duodenum in proper concentration. To support this theory we believed it necessary to demonstrate that when hydrochloric acid of a concentration represented by the peak of the gastric acidity obtained in an individual for a particular gastric meal, entered the duodenum in small quantities, the normal gastric secretion would be depressed. Further, we believed that when acid representing the peak acidities reached in duodenal ulcer patients is instilled, it should fail to produce such depression in those cases which show an extra-gastric curve.

In order to test this view we selected normal and uncomplicated duodenal ulcer subjects. For each we determined the secretory response to a test meal

of 30 gm. of zweibach and 300 c.c. of distilled water. In a few days this was repeated a second time with the standard meal in order to be certain that the test subject did not show any marked fluctuation in acid secretory response. The same length of tube for intubation for each patient was used throughout the series of tests in order to place the tip in as nearly the same area of the stomach as possible. Then with a similar test meal, with one Rehfuss tube in the stomach and another with its tip in the proximal duodenum, we introduced hydrochloric acid in proper concentration very slowly through the duodenal tube as the gastric meal was ingested. Gastric samples were removed at 15 minute intervals as in the standardization procedure and all specimens analyzed for free and total hydrochloric acid and total chlorides. The charts are characteristic of the results obtained.

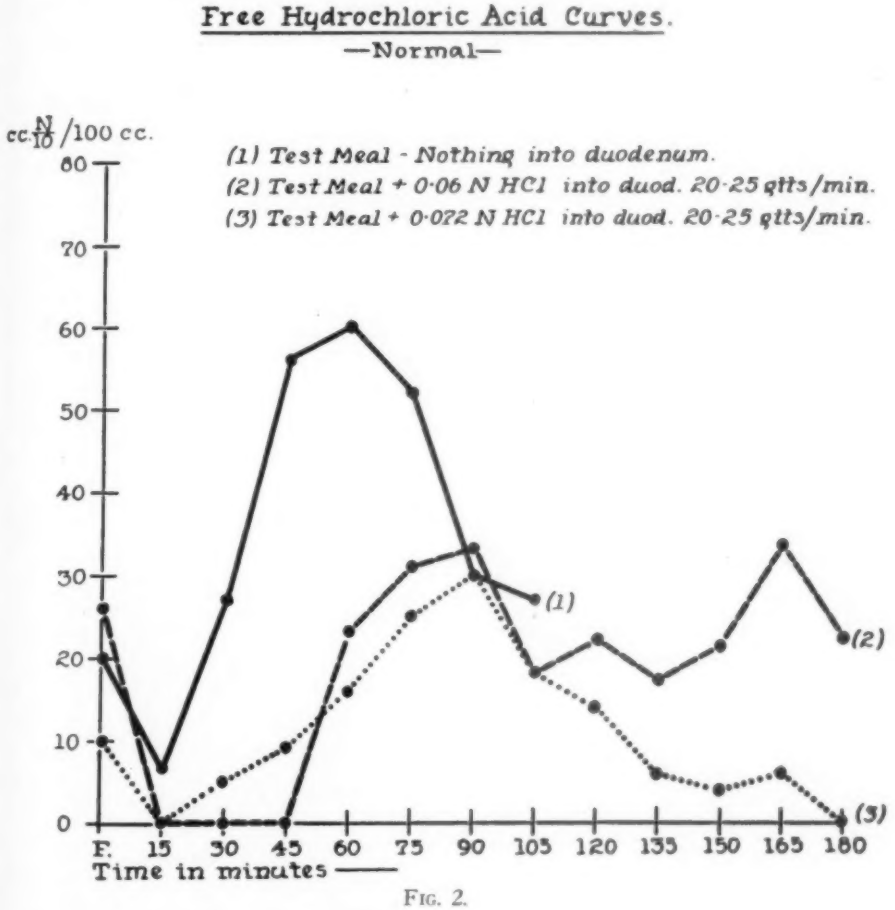

FIG. 2.

In figure 2, curve 1, one sees the response of a normal individual to our test meal. Figure 1, curve 2 shows the marked depression of acidity after a similar test meal when 0.06 N hydrochloric acid was dripped into the duo-

denum at the very slow rate of 20 to 25 drops per minute. When the concentration was increased to 0.072 N on another occasion, figure 2, curve 3, there was no striking change from curve 2. The concentrations of 0.06 N and 0.072 N were selected in this instance because they represented respectively the peak of free and total acidity obtained when the test meal alone was given. The total acid and chloride curves parallel the results recorded for the free acid.

Strikingly different are the results of similar experiments in uncomplicated cases of duodenal ulcer. Figure 3 illustrates the behavior of the free hydrochloric acid response in such a patient. Figure 3, curve 1 is the free hydrochloric acid response to the test meal. Figure 3, curve 2 represents the response to a similar meal when 0.079 N HCl was dripped into the duodenum at the rate of 20–25 drops per minute. The 0.079 N HCl in this instance represented the peak of the free hydrochloric acid seen in figure 3, curve 1. No change either in the peak or character of the free acid curve was produced. On other occasions, we increased the quantity of 0.079 N HCl instilled into the duodenum (figure 3, curve 3) and then the acid introduced into the duodenum was doubled in concentration (figure 3, curve 4). Even with this concentration there is no appreciable difference in the gastric acid curve produced when compared with figure 3, curve 1. Here, too, the total acid and chloride curves parallel the results shown for free acid.

In view of the results demonstrated [1] in our roentgen studies of the influence of hydrochloric acid in the duodenum upon gastric emptying, the difference in gastric motor effect of acid in the duodenum measured by fractional gastric analysis, seen in figures 2 and 3, is of particular interest. The retardation of gastric emptying in the normal individual (figure 2, curves 2 and 3) is very striking when compared with figure 2, curve 1; a change in gastric emptying from 105 minutes for curve 1 to 180 minutes for curves 2 and 3, or an increase in gastric emptying time of 71 per cent. The duodenal ulcer patient on the other hand (figure 3, curves 2 and 3) shows an increase of only 15 minutes in emptying time, a change which certainly must be considered within the limits of experimental error. Curve 4 showed a change of 30 minutes as compared with that obtained in curve 1, an increase of 25 per cent in gastric emptying time. These results corroborate those reported in our roentgen studies [1] and perhaps illustrate in a more quantitative fashion the effect of hydrochloric acid in certain concentrations in the normal duodenum upon gastric motor function and the lack of effect in the duodenal ulcer patient.

In previous studies we have shown [2] that the duodenal mechanism concerned with gastric motor function has a lower threshold of response than the one involved in gastric secretory control. Since we believe that in duodenal ulcer these duodenal mechanisms are depressed and not destroyed, it is of interest to note the more evident effect of the stronger acid solution (figure 3, curve 4) upon gastric emptying.

This duodenal mechanism, too, can explain the low and high gastric secretory normal responses. Although in all bodily functions we recognize an average normal response, we must also concede variants from this average which cannot be classed as pathological. In the same manner, we may

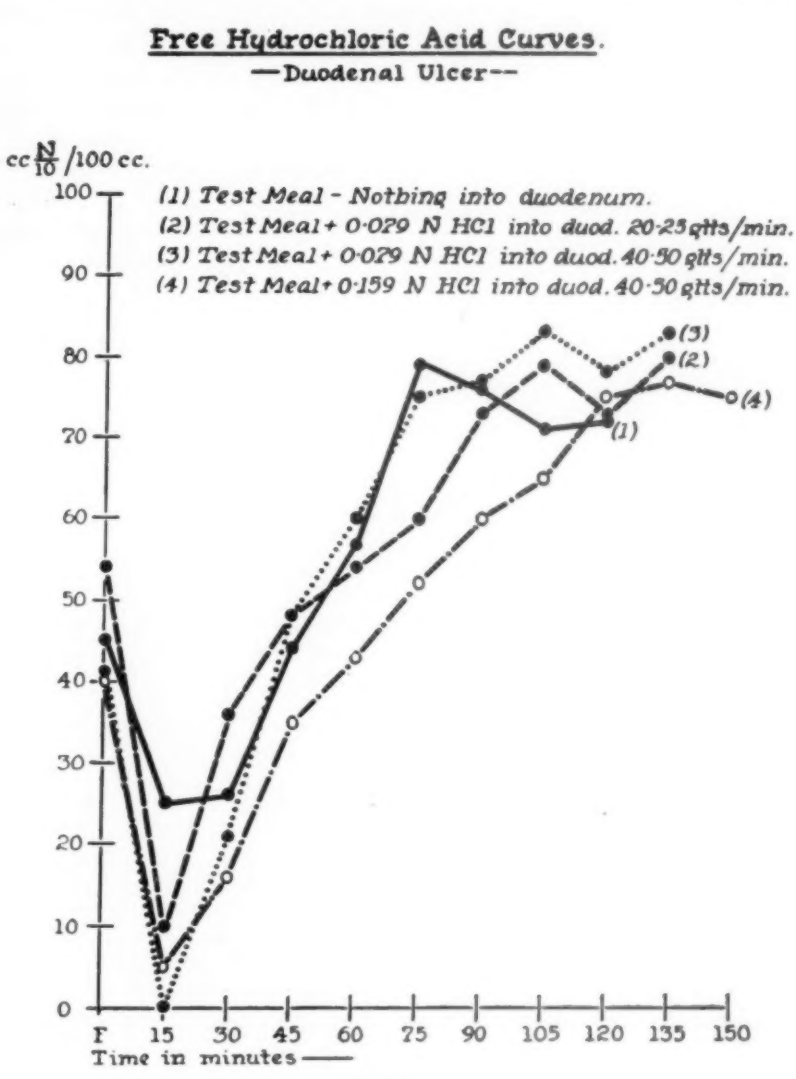

FIG. 3.

postulate variations from the average in the threshold of response. In an individual whose duodenal mechanism has a lower threshold of response, reaction to an acid concentration lower than average should result in a gastric secretory response that is lower. On the other hand, if the threshold of response is higher than average, gastric secretion will not be depressed

through duodenal stimulation until gastric acidity has reached a concentration capable of stimulating the mechanism and a patient with a high gastric secretory response will be found.

This is illustrated in figure 4, a patient who, though normal from all examinations, showed a peak free acidity of 79 clinical units after our test meal, a response that is above the average normal. Yet the instillation of HCl of like concentration into the duodenum at the slow rate of 20–25 drops per minute produced a very sharp depression of gastric secretion after the ingestion of a similar meal.

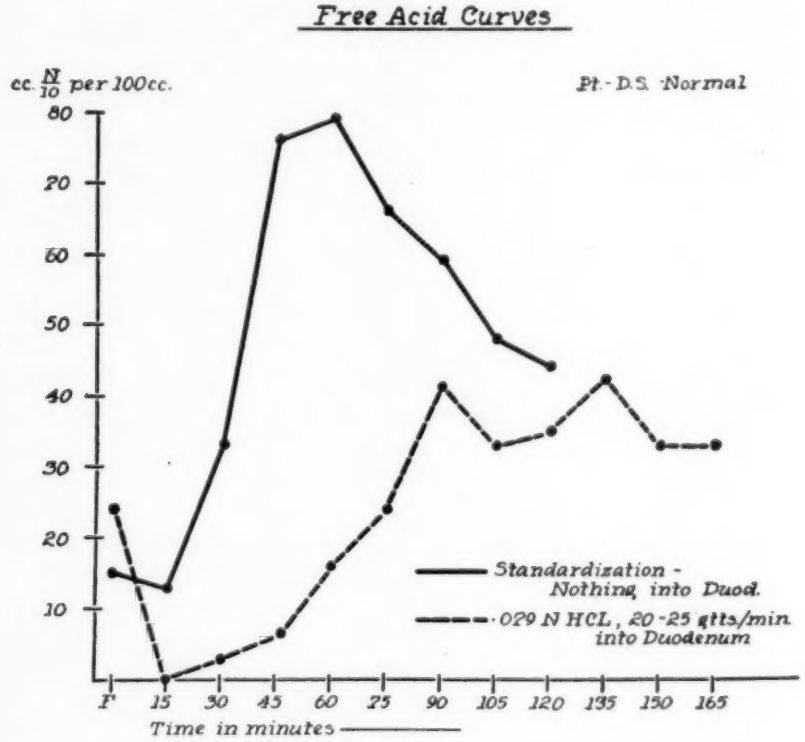

FIG. 4.

Summarizing, we believe that our studies for the first time present data which place in a single disturbed mechanism an adequate explanation for all of the abnormal gastric phenomena seen in uncomplicated duodenal ulcer. We believe that the normal duodenum houses a mechanism which is activated by gastric hydrochloric acid (intrinsic activator) when it reaches the duodenum in proper concentration. This mechanism is responsible for the *local factors* controlling both gastric emptying and gastric secretion. The gastric hydrochloric acid acts as a self-regulator of secretion. Further, we believe that the most active part of this regulating mechanism is located in the duo-

denal cap and proximal duodenum. When this mechanism is depressed by ulceration in the cap and inflammation of the adjacent duodenum, it fails to respond to the normal intrinsic activator when the gastric hydrochloric acid reaches it, resulting in (1) a failure to cause normal pyloric closure and decrease in gastric peristaltic activity and tonus, which result in rapid gastric

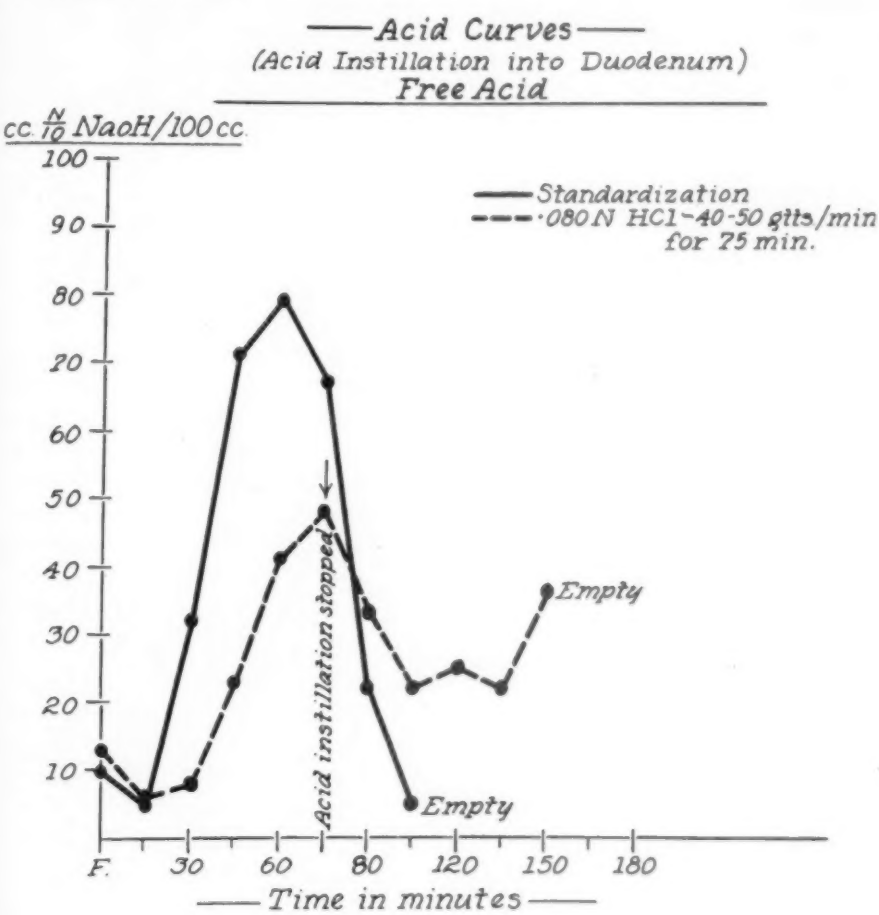

FIG. 5.

motility, hyperperistalsis, and hypertonicity, (2) a failure to put a check to active gastric secretion, with the resultant hypersecretory extra-gastric curve so frequently seen in duodenal ulcer.

In the difference in thresholds of response of the duodenal mechanisms concerned with gastric motor and secretory functions, may lie the explanation of the clinical observation advanced to discredit the rôle of gastric hyper-

secretion as a factor in the chronicity of duodenal ulcer. This observation holds that when duodenal ulcer patients are examined during the period of quiescence, or supposed healing, one frequently finds that although no abnormal gastric motor phenomena may be seen at such times, the gastric secretory response to a particular test meal does not differ in the slightest from the response observed at the time of clinical ulcer activity. We believe the explanation of this fact is as follows: the ulcer healed over, the associated duodenitis gone or diminished, duodenal function returns to a point at which the gastric acid reaching the duodenum is of sufficient concentration to activate the gastric motor mechanism, the one with the lower threshold of response, but not strong enough to activate the partially damaged gastric secretory mechanism, the one with the higher threshold of response.

Changes in the threshold of response of the duodenal mechanism concerned with gastric secretion may explain also the low and high acid gastric secretory responses seen in individuals otherwise normal. Because variations in response are physiological, such patients when tested respond in a normal manner. In duodenal ulcer the mechanism pathologically altered by the ulceration fails to respond to quite active stimulation. That the duodenal mechanism, even in ulcer, is not destroyed, but markedly depressed is shown by the fact that both the motor [4] and secretory [2] duodenal mechanisms can be made to respond to extrinsic stimulants such as fats. Further, we have evidence that the duodenal mechanisms may, in some cases, when the ulcer activity subsides, recover sufficiently to yield a secretory curve that is normal in character although responding at a higher level—a picture similar to the normal high acid individual.

Patient H. A., figure 5, is the same one who gave the results illustrated in figure 3 except that the studies in figure 3 were done at a time when he was having ulcer symptoms. The studies in figure 5 were done five months later during which time he had been on an ulcer régime with resultant clinical quiescence of his ulcer. Figure 3 shows a failure of the duodenal secretory and motor mechanisms to respond to acid stimulation; figure 5 demonstrates a normal type of response in both mechanisms. We believe that the response in figure 5 represents a period of improved duodenal function and an increased sensitivity of the duodenal mechanisms possible during periods of ulcer healing and reduction of associated duodenitis.

We wish to stress again that the above expressed view is concerned only with the local mechanisms in the stomach and duodenum—that, however, we do not forget there is also a "remote control" mechanism for both gastric motor and secretory function; furthermore, that the local mechanism is not activated solely by the "intrinsic" hydrochloric acid but also responds to "extrinsic" agents introduced by food. These, through chemical or physical effects, upon reaching the duodenum may also bring the motor or secretory or both mechanisms into play.

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CASE REPORTS

THROMBOCYTOPENIC PURPURA AND CARCINOMA OF STOMACH; REPORT OF A CASE WITH PURPURA APPEARING AFTER SUBTOTAL GASTRECTOMY *

By WILLARD H. WILLIS, M.D., *Utica, New York*

ISOLATED instances of thrombopenia and purpura associated with carcinoma of the stomach have previously been reported. These cases are of diagnostic interest because the clinical picture is frequently confusing. The initial complaint may be referable to the purpura, and the gastrointestinal symptoms, if present, may be ignored by the patient and the physician. The primary lesion may be small and difficult to diagnose by roentgen-ray as well as at the autopsy table. Even if carcinoma is suspected the characteristically extensive metastatic invasion of the bone marrow and lungs may not be discernible in roentgenograms.

In 1936 Jarcho [11] called attention to the fact that pathologically the cancers which are complicated by thrombopenia, the lymphangitic carcinomas of the lung,[15] and the Krukenberg tumors of the ovary represent a "distinctive variety" of tumor metastasis for which he proposed the name "diffusely infiltrating" carcinoma. As the name implies, there is widespread microscopic invasion of various parts of the body. The lymphatics of the lungs and the ovary and the sinusoids of the bone marrow are common sites of metastasis. If the bone marrow is heavily involved, thrombocytopenia and myelophthisic anemia may occur. The stomach is by far the most common primary site of tumors capable of this type of metastasis.

Purpura and thrombopenia associated with carcinoma are quite unusual. It has even been suggested that the platelet count is usually increased in malignancy.[14]

Fifteen cases of carcinoma of the stomach associated with thrombocytopenic purpura have been found in the literature. Some outstanding clinical features of these are summarized in table 1. Although data now of interest to us frequently are omitted in these reports, there is enough information to suggest some clinical as well as pathological similarities. It will be seen that the patient is usually a young adult having varying degrees of anemia characterized by immature forms in the peripheral blood. Often the carcinoma was not discovered until autopsy. In three cases [6, 10, 13] it was stated that it was difficult at autopsy to determine from the gross specimen if the lesion found in the stomach was malignant. Twice [3, 8] the tumor was found at operation for splenectomy and exploration. In all except two cases (one [6] in which only the tibia was examined and another [8] in which no autopsy was done) there were striking metastases to bone which roentgen-ray at times failed to reveal. In no case was a sternal puncture done.

The lungs were not always described, but in four cases [4, 9, 10, 11] there was microscopically widespread "lymphangitic" involvement. In one [10] there was a typical Krukenberg tumor.

* Received for publication April 26, 1941.

TABLE I

Some Clinical Features of Cases Previously Reported

Author	Age	Sex	Outstanding Complaint	Initial Blood Count	Blood Smear	Metastases	Roentgen-ray Evidence of Metastasis
Schleip [1]	33	M	Hemoptysis, acute, abdominal pain	Plat. "Diminished" R.B.C. 2,944,000 Hgb. 40% W.B.C. 7,200	120 normoblasts and 15 megaloblasts per 100 W.B.C.	Bone, lymph nodes, pleura	Not described
Dünner [2]	37	F	Bleeding tendency and gastro-intestinal	Plat. 12,000 R.B.C. 1,800,000 Hgb. 50% W.B.C. 3,500	Occasional normoblasts	Bone, liver, heart	Not described
Dünner [3]	29	F	Hemoptysis, gastro-intestinal	Plat. 50,000 R.B.C. 3,000,000 Hgb. 45% W.B.C. 7,400	Findings of secondary anemia only	Bone, liver	Not described
Seemann [4]	38	F	Gastro-intestinal	Plat. 150,000 R.B.C. 4,200,000 Hgb. 73% W.B.C. 12,000	Many normoblasts and 2% leukoblasts late in course	Bone, lung, abdominal nodes, pancreas	Not described
Blum [5]	46	M	Gastro-intestinal	Plat. 16,000 R.B.C. 4,000,000 Hgb. 55% W.B.C. 15,000	Normoblasts prominent, 4% myelocytes	Bone, lymph nodes, peritoneum, liver	Not described
Blum [5]	58	M	Widespread pains	Plat. 32,000 R.B.C. 2,080,000 Hgb. 35% W.B.C. 4,600	5 normoblasts per 100 W.B.C., 45% of neutrophiles segmented	Bone, liver, pleura, pancreas	Yes
Steinfield [6]	55	F	Gastro-intestinal	Plat. 66,000 R.B.C. 3,500,000 Hgb. 60% W.B.C. 7,200	Large numbers of normoblasts and immature granulocytes	None (tibia only bone examined)	Not described

TABLE I—(*Continued*)

Author	Age	Sex	Outstanding Complaint	Initial Blood Count	Blood Smear	Metastases	Roentgen-ray Evidence of Metastasis
Kohn [7]	57	F	Debility, gastro-intestinal, purpura	Plat. 10,000 R.B.C. 1,600,000 Hgb. 28% W.B.C. 6,600	6.6% normoblasts, .3% myeloblasts	Bone, lymph nodes, peritoneum	Not described
Stillman [8]	35	M	Gastro-intestinal	Plat. 21,000 Hgb. 65% W.B.C. 12,500	Not described	Abdominal lymph nodes (at operation, no autopsy)	Not described
Lawrence [9]	43	M	Gastro-intestinal	Plat. "markedly diminished" R.B.C. 3,000,000 Hgb. 57% W.B.C. 10,000	4 nucleated R.B.C. per 100 W.B.C., many immature myeloid cells	Bone, lungs, mesenteric glands, adrenals, liver	Roentgen-rays of dorso-lumbar spine negative
Stebbins [10]	21	F	Pain in legs	Plat. 30,000 R.B.C. 2,630,000 Hgb. 50% W.B.C. 11,600	No abnormal cells	Bones, lungs, spleen, ovaries, lymph nodes	Roentgen-rays of pelvis negative
Jarcho [11]	23	M	Purpura and back pain	Plat. 18,000 R.B.C. 3,040,000 Hgb. 58% W.B.C. 4,500	Nothing unusual described	Bone, lungs, liver, lymph nodes	Roentgen-rays of chest, femurs and vertebrae negative
McLeod [12]	32	M	Purpura and acute abdominal pain	Plat. 15,420 R.B.C. 2,570,000 Hgb. 58% W.B.C. 17,400	5 normoblasts per 100 W.B.C.	Bone, liver, lymph nodes, adrenal	Not described
Thompson [13]	45	M	Weight loss, epigastric pain	Plat. 46,000 R.B.C. 2,100,000 Hgb. 44% W.B.C. 9,000	1 normoblast per 100 W.B.C., myelocytes present	Bone, lungs, liver	No definite evidence at first, later bone invasion demonstrated
Thompson [13]	32	M	Weakness, bleeding tendency	Plat. 30,000 R.B.C. 2,600,000 Hgb. 48% W.B.C. 20,000	Numerous nucleated R.B.C., 12% myelocytes	Extensive widespread	Not described

The following case was observed at the Henry Ford Hospital. It is interesting because it is typical of this group in many respects and because purpura, appearing many months after subtotal gastrectomy, was the first clinical manifestation to suggest metastasis.

Case Report

A. S., a 42-year-old woman, first entered the hospital in August 1938, complaining of postprandial upper abdominal distress. Positive findings were roentgen-ray evidence of a persistent filling defect in the pyloric antrum, gastric hypoacidity and occult blood in the stools.

A subtotal gastrectomy was performed by Dr. Roy D. McClure, August 21, 1938. An area of about 5 cm. in diameter in the antrum was polypoid and firmer than the adjacent tissue. In this area the mucosa was for the most part replaced by typical glands, columns and masses of neoplastic cells (figure 1). Throughout the remainder

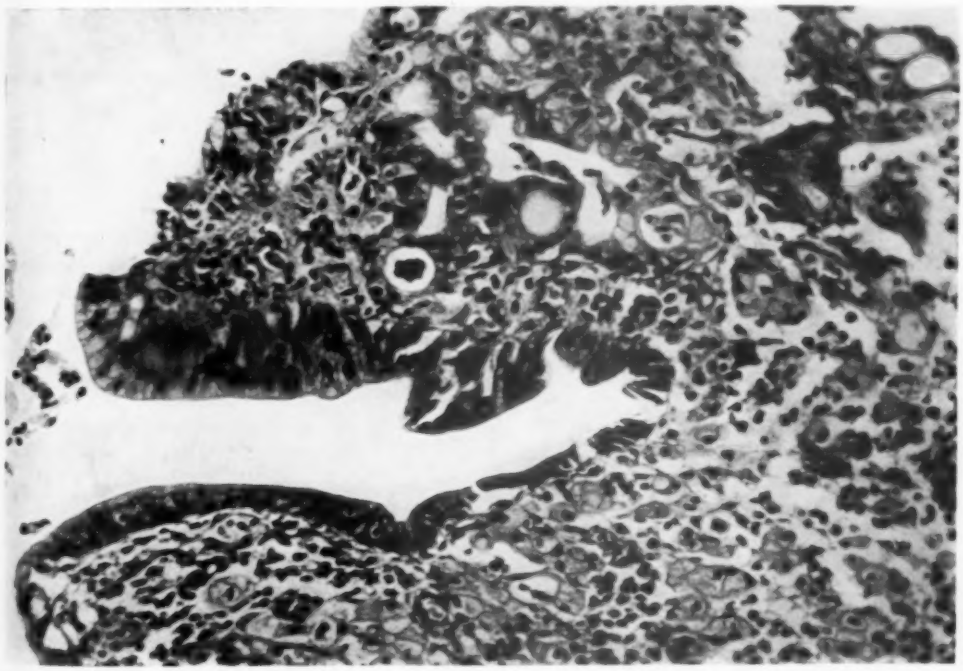

Fig. 1. The margin of the malignant pyloric ulcer which was resected a year prior to the patient's death.

of the wall, however, compressed alveoli or single cells invaded the stroma almost like inflammatory cells. A mesenteric lymph node contained malignant cells.

The patient remained well until the following May when she began to have pain in the lower extremities associated with purpuric lesions. In June 1939, she was admitted to the hospital again where she remained until her death late in August, just a year following the gastric resection. The blood count upon admission was: erythrocytes 3,500,000; hemoglobin 10.5 gm.; leukocytes 8,000; and platelets 50,000. An occasional normoblast appeared in the peripheral blood. Menorrhagia became an alarming symptom. Frequent blood transfusions and other forms of symptomatic treatment failed to bring about improvement.

Ten weeks prior to death, roentgen-rays of the lumbo-sacral spine failed to show evidence of metastasis. Roentgen-rays of the chest and long bones, three and two weeks prior to death respectively, were negative.

An autopsy was done by Dr. Frank W. Hartman. The only gross metastases were in the abdominal lymph nodes. Microscopically, however, there was involvement of the lungs, the bone marrow, an adrenal and the liver. The bone marrow of the sternum and lumbar vertebrae was extensively invaded by strands and masses of cells resembling the structure of the original tumor (figure 2). The tumor cells were supported by a fibrous stroma almost completely devoid of normal marrow cells. Tumor was not present in some sections taken from the lumbar vertebrae. Here the marrow spaces contained a loosely arranged fibrous stroma; few normal cells were seen. The findings in the lungs were also striking. In many sections the lymph spaces were filled with malignant cells but nowhere was there alveolar destruction. The ovaries were not invaded.

FIG. 2. Showing diffuse infiltration of bone marrow by tumor cells.

SUMMARY AND DISCUSSION

A case of thrombocytopenic purpura secondary to replacement of bone marrow by a diffusely infiltrating carcinoma having its origin in the stomach is reported. It is distinctive because the purpura was the first symptom to suggest metastasis.

Thrombopenic purpura of obscure etiology should lead one to suspect the presence of a diffusely infiltrating carcinoma which commonly has its origin in the stomach. Likewise, in a person known to have or have had carcinoma of the stomach the appearance of purpura should suggest the possibility that this type of spread has occurred.

Roentgen-ray is not a reliable means of demonstrating the metastases either in the lungs or in the bone marrow. Studies of sternal marrow, however, should be of diagnostic value.

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THE WATERHOUSE–FRIDERICHSEN SYNDROME: REPORT OF A CASE IN AN ADULT *

By A. T. Kwedar, M.D., *Springfield, Illinois*

The presence of purpuric or petechial spots on the skin, associated with a massive hemorrhagic destruction of both adrenals and the presence of a fulminating septicemia, is recognized as the Waterhouse-Friderichsen syndrome.[1]

Seventy per cent of all cases reported are in children under the age of two years. This may be owing to the susceptibility and lack of immunity of children to the meningococcus. In Aegerter's [2] review of the literature he found only six cases of Waterhouse-Friderichsen syndrome occurring in adults, only three of whom were over 50 years of age. Foucar,[3] in 1936, reported one case in a 20 year old male and since that time all cases reported have been in children.

* Received for publication August 6, 1940.

Including the case herein reported there are now about 77 cases of this syndrome in the literature. Kunstadter [4] brought the literature to date in 1939, and there has been added one case by Levinson [5] and two by McNamara and Connell.[6]

Case Report

A. S., a housewife, aged 58 years, was first seen in her home at 2 p.m. on January 15, 1940. Her complaint was a mild upper respiratory infection of about 10 days' duration. She had been up and about doing her housework until the last two days, when she began to feel chilly and perspire freely. On the day of examination she felt a pain in her right ear and complained of nasal obstruction with a slight discharge.

Examination revealed a fairly obese white woman, not acutely ill. Temperature was 100.4° F.; pulse rate 94 per minute, respirations 20 per minute, and blood pressure 150 mm. Hg systolic and 84 mm. diastolic. Head: There were two or three petechiae in the lower conjunctiva of each eye. The pupils were round and equal and reacted to light. The turbinates were swollen; the maxillary and frontal sinuses transilluminated light and were not tender. The left ear drum was normal; the right was not inflamed, but there was a hemorrhagic area in the posterior-superior part of the drum and the inner canal wall. The patient was edentulous. The tonsils were absent. Neck: The left tonsillar lymph node was slightly enlarged and tender. Chest: The lungs were clear to percussion and auscultation. The heart rhythm was regular, and the tones clear; no murmurs were heard. The heart borders were within normal limits. Abdomen: A healed surgical scar was present in the right upper quadrant (a cholecystotomy had been done on September 6, 1939). There were no palpable masses and no tender areas. A left inguinal hernia was present. Reflexes: There was no sign of meningeal irritation. The knee jerks were physiological and there was no Babinski.

Enteric-coated ammonium chloride, aspirin, a cough mixture, and a nasal spray of ephedrine sulfate were prescribed.

About 3 p.m. of the same day the patient began to vomit; this continued all afternoon. She began to have diffuse pain in the abdomen, for which she took an enema that gave no relief. At 7 p.m. the patient was sent a prescription containing morphine sulfate, bismuth subnitrate, and cerium oxalate in syrup of acacia to allay the vomiting. It stopped shortly after taking of the medicine.

The patient was seen for the second time at 10 p.m. of the same day. She now complained of a burning sensation in the thighs and back. She appeared very weak; pulse was soft and regular, 98 per minute; temperature was 101° F.; respirations were 30 per minute. Numerous petechiae were present in the conjunctivae. The hemorrhagic area in the right auditory canal remained about the same. The skin of the chest had numerous petechiae, varying in size from pin-point to pin-head. The skin of the back presented a diffuse purplish hue and white dermatographism was marked. The abdomen was silent and there was no localized tenderness. The lungs were resonant, but a few fine crepitant râles were present at the bases and expansion seemed to be somewhat restricted. The heart tones were very distant; the blood pressure was 78 mm. Hg systolic, 50 mm. diastolic. She was given 12 minims of adrenalin and taken by ambulance to St. John's Hospital.

Upon admission to the hospital she was given two ampules of coramine and one of caffeine sodio-benzoate. She was also given ¼ grain of morphine sulfate, for she was complaining bitterly of burning of the skin of the thighs and was crying for relief. A vaginal examination revealed the corpus to be anterior and of normal size. A bedside film of the chest showed the lungs to be essentially negative except for a slight haziness at the base of both lung fields. Another ¼ grain of morphine sulfate was given for pain, and intravenous therapy was started with 1000 c.c. of 5 per cent

glucose in normal saline. Five grains of sodium phenobarbital were given directly into the tubing of the intravenous set for severe restlessness.

A blood count taken about midnight revealed: Hemoglobin 14 gm. per 100 c.c.; red blood count 4,000,000; white blood count 17,000. Differential count showed polymorphonuclears 65 per cent, large lymphocytes 3 per cent, small lymphocytes 32 per cent. Slight anisocytosis and poikilocytosis of the red blood cells were present. Intracellular and extracellular diplococci were present in the blood smear (figure 1). A Gram stain of another smear showed this organism to be Gram negative. A blood culture later, indicated that the organism was a *Neisseria intracellularis* (meningococcus).

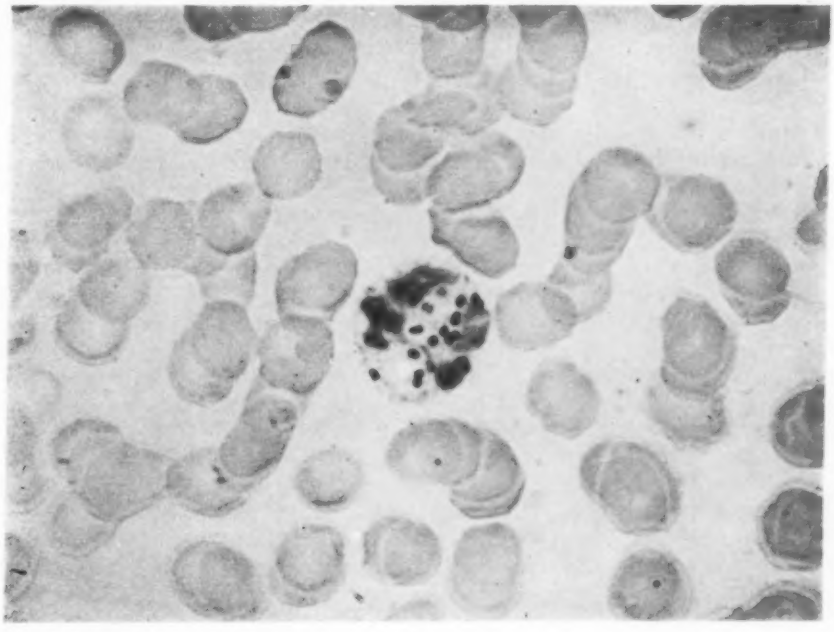

FIG. 1. Blood smear taken two hours before death, showing intra-cellular meningococci. Wright stain. 1035 ×. (Photomicrograph by Dr. Aloysius Vass, Pathologist of Springfield Memorial Hospital.)

The patient was then given 20 c.c. of a 5 per cent solution of neoprontosil subcutaneously and 5 c.c. additional intravenously.

Her pulse was rapid and thready. Blotches appeared over the entire face, chest, abdomen and legs; here numerous petechiae and ecchymoses were present, some developing while the patient was being observed. The dependent skin assumed a peculiar blotchy lividity. The patient at 1:15 a.m. was still conscious, respirations were rapid, and she cried out incessantly that her skin was "on fire," especially that of the thighs and back. She was given ½ grain of morphine sulfate and a final dose of five grains sodium phenobarbital intravenously. Restlessness was still present, even though she had received a total of one grain of morphine and 10 grains of sodium phenobarbital intravenously. At 1:30 a.m. she began to froth at the mouth and became cômatose. She died at 2:10 a.m., January 16, 1940 (12 hours from the time she was first seen).

Autopsy (limited to an abdominal incision).* The body had already been completely embalmed. There was noted a very striking blotchy purplish mottling of the entire skin surface. There also appeared to be a considerable diffuse edema, especially of the face.

The most striking gross changes were noted in the adrenals. The right adrenal measured 6 by 3.2 by 1.2 cm., and weighed 9 gm. It was well preserved, in contrast to the left. The right adrenal was firm in consistency, but had a very dark red color throughout. It was surrounded by a large amount of rather adherent fat. On the cut surface, the cortex and medulla were readily distinguishable from each other and appeared to be of ordinary thickness. The dark red discoloration involved both medulla and cortex.

The left adrenal was considerably softened and had been torn to some extent by the embalmer's trocar. It was estimated that it must have had about the same dimensions and weight as the right adrenal. In the best preserved portions of the left adrenal the same very marked discoloration could be found as has already been described in the right.

Microscopic examination of both adrenals showed very extensive massive hemorrhage, with almost complete destruction of all of the tissue elements. The medulla, as far as could be determined, was completely destroyed. In the cortex at most places nothing could be found but large amounts of fresh blood, the original structure being represented only by remnants of connective tissue framework. In some places groups of cortical cells could still be discerned. The latter usually had opaque cytoplasm and possessed relatively large, rather faintly stained nuclei. Bacterial stains of these sections showed large numbers of Gram negative diplococci. Some of these apparently were free in the extravasated blood, whereas others were found within polymorphonuclear leukocytes. Similar organisms were seen within some of the swollen cells of the adrenal cortex. The adrenals were the only internal organs in which hemorrhages were noted.

Sections of the skin were taken through some of the discolored blotches noted grossly. There was present an intact epidermis of ordinary structure. Beneath it was a collagenous corium showing edema. All of the smaller blood vessels of the corium were considerably engorged, but no actual extravasation of blood could be demonstrated anywhere. Around a few of the engorged veins a little polymorphonuclear infiltration could be detected. Microörganisms could not be demonstrated in these sections.

The lungs showed pulmonary edema. There was an early acute myocarditis, as shown by the presence of a little diffuse polymorphonuclear infiltration of the myocardium. In the liver there was noted considerable fatty metamorphosis. The other organs showed nothing of particular interest.

Comment

The above case is reported because of the relatively infrequent occurrence of this syndrome in adults and also because of the paucity of reported antemortem bacteriological examinations. Although McLean and Caffey [7] report the finding of positive blood smears taken from purpuric lesions of the skin in 83 per cent of cases of meningococcus meningitis, in the above patient the blood stream was overwhelmingly infected and ordinary smears taken from the finger contained numerous intracellular and extracellular meningococci. It was noted that considerable difficulty was encountered in obtaining blood from a stab wound of the finger, apparently owing to the marked hypotension.

* Performed by Dr. F. W. Light, Pathologist of St. John's Hospital.

The essential pathologic change noted was a complete destruction of the medulla of both adrenals, with only scattered remnants of cortical tissue framework remaining. Bacterial stains showed the meningococci present in the adrenals. Sections of the purpuric skin lesions showed only engorged blood vessels of the corium with no actual extravasation of blood.

Clinically the patient presented a picture, at the onset, of an ordinary upper respiratory infection. Chills and fever soon followed, with petechiae and purpuric lesions of the skin. Then there appeared vague abdominal pain and vomiting, soon after which the patient presented a picture of severe circulatory collapse. While crying out with burning pain in the skin, she died within 12 hours of the onset.

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3. Foucar, F. H.: Acute fulminating meningococcus infection with bilateral capillary hemorrhage of the adrenals as the most striking gross pathologic lesion; a case report, Ann. Int. Med., 1936, ix, 1736–1746.
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7. McLean, S., and Caffey, J.: Endemic purpuric meningococcus bacteremia in early life: diagnostic values of smears from purpuric lesions, Am. Jr. Dis. Child., 1931, xlii, 1053–1074.

EDITORIAL

CRUSH SYNDROME

THE occurrence of fatal renal insufficiency following crush injuries of the limbs was first clearly described by Bywaters and Beall [1] in 1941, who reported four cases and described a typical clinical syndrome. Their observations have since been confirmed by a number of other British writers.

These cases were all victims of bombing disasters and had been buried several hours under the debris of wrecked houses in such a manner that the muscles of the limbs or trunk had been subjected to intense pressure. On release, in some cases there was evidence of severe local trauma, with weals like those following burns, abrasions, ecchymoses, and even incipient gangrene, with some local edema. More often evidence of local injury was slight, and there might be merely some local erythema, so that the serious nature of the injury is easily overlooked. According to Patey [2] the syndrome may follow simple compression without actual crushing of the muscle. A similar condition has been reported following motor accidents, after compound fractures of the leg, and after protracted, difficult labor.

Within a few hours the injured limb became markedly swollen. The tissues at the site of compression became intensely indurated, and softer edema extended over the entire limb and often onto the trunk. Probably as a result of the edema, the patient was unable to move the limb, there were paresthesias or anesthesia, and arterial pulsation was partly or completely obliterated.

When first released, patients might be in shock, but as a rule their condition was good. Shock developed some hours later, with a fall in blood pressure and acceleration of the pulse rate. This was accompanied by sweating and evidences of dehydration, a high hemoglobin content and some rise in plasma protein. Shock was combated successfully by means of injections of serum or plasma or by transfusions, and the patients were rarely in shock for more than a few hours. It did not appear to be a major factor in the production of the subsequent renal failure.

In spite of recovery from acute shock, oliguria appeared quickly and in the severe cases became extreme, even to the point of complete anuria. There was some general edema, thirst, often persistent vomiting, with anxiety or drousiness. Death occurred in uremia, usually on the fifth to the eighth day.

The urine at first was often rusty in color, and it contained albumin, red blood cells and many pigmented casts. Later the albumin and the formed elements tended to disappear, but the urine was pale and the specific gravity

[1] BYWATERS, E. G. L., and BEALL, D.: Crush injuries with impairment of renal function, Brit. Med. Jr., 1941, i, 427.

[2] REPORT OF THE ROYAL SOCIETY OF MEDICINE, SECTION OF SURGERY: Effects on the kidney of limb compression, Brit. Med. Jr., 1941, ii, 884.

and urea concentration were low. The concentrating power and the capacity to reabsorb chlorides were markedly impaired. It resembled a glomerular filtrate. The most striking changes reported in the blood were a progressive rise in blood urea to 140 mg. per cent or higher and in the serum potassium to about 25 mg. per cent. Patients who recovered showed, after about a week, a gradual fall in blood urea and an increase in the volume and specific gravity of the urine.

At necropsy the significant changes noted were largely limited to the muscles and to the kidneys. The muscles showed local necrosis of varying degree and often patchy hemorrhages. A striking feature was marked pallor of the injured muscle, like "fish flesh," resembling the changes seen in paralytic myoglobinuria of horses.[3] There was marked edema, so that the muscle tissue was under great tension within the fascial compartments.

The kidneys were swollen and edematous. The glomeruli showed little or no change. The tubular epithelium showed degenerative changes which were especially marked in the ascending limb of the loop of Henle and in the distal convoluted portion. The cells showed basophilic cytoplasm, pyknosis of the nuclei, or actual necrosis. The lumina of many of the tubules were blocked by orange colored or dark brownish granular casts made up of or containing hemoglobin-like pigment. These casts were also found in some of the collecting tubules in the medulla. Dunn et al.[4] have described (in two cases) peculiar lesions in the ascending limb of Henle's loop in the boundary zone between the cortex and medulla. These consisted of aneurysmal dilatations of the tubule, 40 to 80 micra in diameter, filled with albuminous material. These tended to rupture into the interstitial tissue or into an adjacent venule and extrude the albuminous contents. There was also evidence of regeneration and proliferation of epithelial cells. The lesions, in general, resembled those seen in some cases of experimental tubular nephritis. The location of these lesions has been attributed to a change to an acid reaction of the urine at this level.

The exact pathogenesis of the renal injury has not been definitely established. Shock undoubtedly may contribute to the early oliguria. Many of these cases, however, had not shown severe or prolonged shock. Furthermore lesions of this type were not seen in cases suffering from shock as a result of injuries of other types.

The lesions resembled those which followed transfusions of mismatched blood, and many of the cases had been transfused. However, they did not show the usual symptoms of transfusion reactions, and a number of them had received only plasma or serum, not whole blood. The blood plasma of the patient, in a few cases in which it was examined, was not high colored.

The syndrome is most easily explained on the hypothesis that the kidneys

[3] GILMOUR, J. H.: Myoglobinuria and crush syndrome (letter to editor), Lancet, 1941, i, 524.

[4] DUNN, J. S., GILLESPIE, M., and NIVEN, J. S. F.: Renal lesions in two cases of crush syndrome, Lancet, 1941, ii, 549–552.

are injured by toxic substances liberated from the damaged muscle. It is not yet certain, however, just how this is brought about. The resemblance to myohemoglobinuria of horses is emphasized by the demonstration by Bywaters and Deloy [5] that the pigment in the urine of two cases of crush syndrome gave the spectrum of oxymyohemoglobin. The spectrum of the carboxy- and meta-derivatives also corresponded to those of myohemoglobin.

The disease in horses occurs in animals which have been rested for a few days on a full carbohydrate-rich diet, shortly after they have been put back to heavy work. The animals become lame and may be unable to stand or walk. The muscles feel indurated and the urine is highly colored with myohemoglobin. Death often follows after a few days. The muscles are very pale, like fish flesh, and show degenerative changes and necrosis. Pigmented casts are found in the kidney tubules. Carlström reported finding an excess of glycogen in the muscles. The changes have been attributed to an excess production of lactic acid, together probably with some impediment to the local circulation. Gilmour believes that a similar mechanism is concerned in the development of the peculiar muscle lesions in crush syndrome.

A condition similar to the disease of horses has been reported as a great rarity in man. In one case quoted by Bywaters,[5] exercise was followed by a rise in plasma potassium, such as occurs in cases of crush syndrome, suggesting an increased permeability of the muscle cells. Similar degenerative changes in the muscles with myoglobinuria have been reported from Königsberg in human cases who had eaten fish poisoned by resinous acids, the by-products of cellulose factories.

Whether or not myohemoglobin is itself directly toxic has not been proved. Mere blockage of the tubules by casts does not seem an adequate explanation. There seems to be also a diffuse toxic injury to the tubular epithelium. In all probability the toxic substance arises in the injured muscles.

Thus far no type of treatment has been shown to be effective. The procedures used have been based, for the most part, on the theory that the disease is caused by toxic substances liberated from the muscles. Shock should be combated by the use of plasma or serum rather than whole blood. McMichael [2] suggested applying a tourniquet proximal to the injury and packing the limb in ice immediately after release to retard the penetration of toxic substances into the circulation. Attempts have been made to secure diuresis by forcing fluids, by mouth if possible, and by vein as glucose or salt solution. In one case, however, extreme oliguria persisted, in spite of the administration of 25 liters of fluid during a period of several days. Among other procedures suggested have been the administration of alkalis; the use of suprarenal cortical extract on the assumption that the high blood potassium indicated a cortical insufficiency; decapsulation of the kidneys, which

[5] Bywaters, E. L. G., and Deloy, G. E.: Myohemoglobinuria (letter to editor), Lancet, 1941, i, 648.

has been followed by recovery in a few cases of anuria following mismatched transfusions; local decompression by incisions to release edema and lower tension; and amputation. In one case reported by Bywaters, however, amputation 36 hours after admission to the hospital did not alter the course of the disease, and the patient died in uremia several days later.

The mortality in outspoken cases was high. Bywaters stated that death occurred in two thirds of the cases who were observed in hospitals. There was no close relationship between survival and the duration of compression or the conspicuousness of the superficial evidences of trauma, although the extent of the injury is important. Recovery did occur in spite of marked oliguria and azotemia.

Improvement in treatment depends upon obtaining a precise knowledge of the pathogenesis of the renal injury. This can probably be secured only by the experimental production of the disease. The problem does not appear to be very difficult, and its solution should be of great practical value in the present emergency.

BOOK REVIEWS

Clinical Roentgenology of Pregnancy. By WILLIAM SNOW, M.D. 178 pages; 26 × 17 cm. Charles C. Thomas, Springfield, Illinois. 1942. Price, $4.50.

This book, according to the author, is an attempt to clarify and simplify the subject of roentgen pelvimetry and cephalometry. In this he succeeds very well, his explanation of the technic being clear and easily understood. The book is evidently written for the roentgenologist and obstetrician, more for the former, and should be a great help to one with a general knowledge of roentgen-ray technic who is just entering upon the comparatively new subject of pelvimetry, cephalometry and soft tissue diagnosis by the roentgen-ray.

The author emphasizes the safety of the roentgen-ray in pregnancy, in the dosage used for diagnosis. He apparently feels that there is no need for roentgen examination as a routine, but that it should be reserved for those cases in which an abnormality is suspected.

The Caldwell and Moloy classification of pelves is followed, which appears to be the best we have to date and the most generally accepted.

The section on soft tissue diagnosis is very well done, and the author's claims in this field are quite modest.

The principal criticism concerns the section on the mechanism of labor, which differs somewhat from that generally taught and leaves something to be desired.

The entire book is profusely illustrated with clear and concise reproductions of films, and the last one third consists of case reports in which all of the films are reduced equally, the original being four and one half times the size of the reproduction. This is in order "that the reader may practice making the measurements."

L. H. D.

Manual of Clinical Chemistry. By MIRIAM REINER, M.Sc. 282 pages; 18 × 13 cm. Interscience Publishers, Inc., New York. 1941. Price, $3.00.

This pocketsized manual of some 280 pages is quite comprehensive and covers the subject of clinical chemistry quite comprehensively. It is designed primarily to correlate routine analysis with clinical observation.

The first section is devoted to a discussion of the fundamental principles of quantitative analysis and the "rules of the game" so to speak. In successive chapters the author in concise yet complete fashion describes the principles, procedures, and reagents utilized for most of the methods used in a clinical laboratory. Each procedure is accompanied by a reference to the original work on the subject.

The reviewer found particularly interesting and helpful the sections on toxicological procedures and those describing the various functional tests. On the whole the methods are the classical procedures with such modifications as the author has found satisfactory.

The busy practitioner or technologist who is interested only in the methods of clinical chemistry should find this little volume invaluable.

E. J. P.

The Autonomic Nervous System. By JAMES WHITE, M.D., and REGINALD SMITHWICK, M.D. 469 pages; 24 × 16 cm. The Macmillan Company, New York. 1941. Price, $6.75.

The second edition of *The Autonomic Nervous System*, written by James C. White and Reginald Smithwick, will be a splendid contribution to the medical libraries of the

country. The authors have brought together in an impartial manner the available facts on this important subject and pictured them in simple language and illustrations. The anatomy and physiology, as well as the clinical facts relating to the system, are so clearly portrayed that they can be readily understood by the advanced student in medicine or surgery. Although the advanced student in the neurological field may not agree with the authors in all details, he will not find them far afield in the fundamentals. It is indeed fortunate, as well as timely, that this comprehensive edition should appear on a subject that is so little understood by the medical profession in general.

After a careful review of the book I heartily recommend it to the practitioners of all branches of the medical profession.

T. B. A.

The Proceedings of the Charaka Club. Volume X. 260 pages; 23.5 × 15.5 cm. Williams and Wilkins Company, Baltimore. 1941. Price, $5.00.

From one of the essays in this book by Dr. Bernard Sachs, entitled "Early Years of the Charaka Club," we learn that this organization is composed of physicians interested in the cultural aspects of medicine. There were five original members who effected the organization of the club in 1899. The present volume is the tenth of the "Proceedings" of the club. It is understood that the first two volumes are scarce.

This book is composed of 23 papers read before the club. The historical essays include papers on Barbara Fritchie, and Dr. William Tyler who was a member of the United States Sanitary Commission during the Civil War. Literary papers of medical interest are represented by such titles as "Fig Leaves for Shakespeare and Montaigne," "The Mystery of Robert Seymour" who illustrated Dickens' "Pickwick Papers," and "A Note on the Satirical Writings of Richard Grant White."

Papers on artistic subjects include "Ramblings of a Rug Addict," "The English Garden," and "Life and Death Masks." Medical history is well represented by the following papers: "Galen on Malingering, Centaurs, Diabetes and Other Subjects," "A Little Book on Children and How It Grew" (This describes "De Aegritudinibus Infantium" of Leonello Faventino de Victoriis [Ingolstadt 1544]); and "The Medical Notions of a Roman Gentleman in the Second Century, A.D."

The book is attractively printed and is delightful to read.

J. E. S.

COLLEGE NEWS NOTES

New Life Member

Dr. Maurice Lewison, F.A.C.P., Chicago, Ill., became a Life Member of the American College of Physicians on March 17, 1942.

Gifts to the College Library

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

Books

Dr. Edward S. King, F.A.C.P., Winston-Salem, N. C.—"Bacteriology Laboratory Methods";
Dr. Francis P. McNamara, F.A.C.P., Dubuque, Iowa—"Collected Reprints and Bibliography of the Finley Hospital Medical Staff, 1927–41";
Dr. Cecil Striker, F.A.C.P., Cincinnati, Ohio—"First Annual Proceedings of the American Diabetes Association";
Dr. Zolton T. Wirtschafter (Associate), Cleveland, Ohio—"Diabetes Mellitus."

Reprints

Dr. Robert S. Berghoff, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Edward G. Billings, F.A.C.P., Denver, Colo.—1 reprint;
Dr. Allen H. Bunce, F.A.C.P., Atlanta, Ga.—3 reprints;
Dr. Guy W. Carlson, F.A.C.P., Appleton, Wis.—1 reprint;
Joseph R. Darnall, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint;
A. Allen Goldbloom, F.A.C.P., Major, (MRC), U. S. Army—1 reprint;
Dr. Isidore W. Held, F.A.C.P., New York, N. Y.—2 reprints;
Dr. LeMoyne Copeland Kelly, F.A.C.P., New York, N. Y.—3 reprints;
Dr. Donald S. King, F.A.C.P., Brookline, Mass.—8 reprints;
Dr. Charles J. Koerth (Associate), San Antonio, Tex.—2 reprints;
Dr. Nils P. Larsen, F.A.C.P., Honolulu, T. H.—1 reprint;
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—2 reprints;
Dr. Louis Bonner Owens, F.A.C.P., Cincinnati, Ohio—1 reprint;
Dr. Herbert J. Schattenberg (Associate), New Orleans, La.—27 reprints;
Dr. Harry W. Shuman, F.A.C.P., Rock Island, Ill.—1 reprint;
Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Merritt Henry Stiles, F.A.C.P., Philadelphia, Pa.—6 reprints;
Dr. F. Erwin Tracy, F.A.C.P., Middletown, Conn.—1 reprint.

We also acknowledge receipt of thirty-seven reprints from Evans Memorial, Massachusetts Memorial Hospitals, Boston, many of which were written by members of the College.

Regional Meeting of Western Pennsylvania Members

Under the Governorship of Dr. R. R. Snowden, F.A.C.P., Pittsburgh, the Fellows and Associates of the College in Western Pennsylvania held their annual regional

meeting, March 25, 1942. At the scientific session conducted during the afternoon there was a demonstration of the electron microscope. The demonstration consisted of informal discussions as to the physical principles and the mechanism of the instrument, and the technic of the preparation and magnification of the specimens. Each member was given an opportunity to view the actual image. After the demonstrations there were further discussions of the use of the electron microscope in the various fields of science, including medicine. Dr. William S. McEllroy, F.A.C.P., Dean of the University of Pittsburgh School of Medicine, presided, and Charles S. Smith, Jr., Ph.D., and Donald A. Wilson, Ph.D., both of the Department of Physics of the University, participated in the discussions.

The scientific session was followed by cocktails and dinner. After dinner the members were shown moving pictures of "Pearl Harbor," "The Normandie," and "Russia Stops Hitler."

Montana A. C. P. Members Hold Regional Meeting

The Montana branch of the American College of Physicians met in Missoula, February 21–22, 1942, this being the seventh annual meeting of this group.

Dr. Fred Schemm, F.A.C.P., of Great Falls, presented a paper on "The Treatment of Edema"; Dr. H. R. Cox, of the U. S. Public Health Service Laboratory, Hamilton, Mont., presented a paper with kodachrome illustrations on his work with "Encephalitis"; and Dr. M. V. Hargett, also of the U. S. Public Health Service Laboratory at Hamilton, presented a paper on "Yellow Fever."

On February 22 the members were the guests of Dr. R. R. Parker and staff at Hamilton, Mont., where the group was conducted through the U. S. Public Health Service Laboratory and where they saw vaccine produced for yellow fever, Rocky Mountain spotted fever, and typhus fever. This laboratory is the second largest public health laboratory in the world.

General arrangements for this regional meeting were made by Dr. Ernest D. Hitchcock, F.A.C.P., College Governor for Montana; Dr. Allen R. Foss, F.A.C.P., of Missoula, Secretary of the Montana group; Dr. Paul Ritchey, F.A.C.P., of Missoula; and Dr. Meredith Hesdorffer (Associate), of Missoula.

Regional Meeting of Western New York Members

Under the Governorship of Dr. Nelson G. Russell, Sr., College Governor for Western New York, a Regional Meeting of the College members from that district was held in Buffalo, Saturday, March 28, in connection with the Eighth Annual Clinical Day of the Alumni Association of the University of Buffalo School of Medicine. The program began at 9:00 a.m., and consisted of clinical lectures by local and guest clinicians. Dr. Philip S. Hench, F.A.C.P., of the Mayo Clinic was one of these. In the evening the members were the guests at dinner of Governor Russell. It is hoped that this initial endeavor will be expanded and conducted in the future.

Regional Meeting of Georgia Members

Under the Governorship of Dr. Glenville Giddings, the first Regional Meeting for Georgia members of the American College of Physicians was held on Saturday, March 14. Of a total membership of 83 in the State, 8 of whom are in military

service, 58 members were in attendance. Among the guests were Dr. Fred W. Wilkerson, F.A.C.P., Governor for Alabama; Dr. Turner Z. Cason, F.A.C.P., Governor for Florida; and Dr. Charles Hartwell Cocke, F.A.C.P., Chairman of the Board of Governors and Governor for North Carolina. The program was as follows:

Scientific Session

2:00 p.m.

Fulton County Academy of Medicine
West Peachtree St.

Effects of Sulfonamide Drugs on the Blood.....Roy Kracke
Policies of the American College of Physicians.....James E. Paullin, President-Elect
Modern Views About the Treatment and Control of Hookworm Disease
Justin Andrews
Pulmonary Edema.....Eugene A. Stead, Jr.
Military Psychiatry in the Present War..Major Ernest Parsons, Medical Corps, U.S.A.
Blood Replacement Therapy in the Armed Services
Major Douglas B. Kendrick, Jr., Medical Corps, U.S.A.

Dinner

7:30 p.m.

Capital City Club

Address: "Experiences on the Burma Road"
Colonel Louis L. Williams, Jr., U. S. Public Health Service

Members were most enthusiastic, both about the scientific session in the afternoon and the dinner meeting in the evening, and have endorsed the plan of holding these regional meetings annually.

Dr. Roger I. Lee, F.A.C.P., Boston, Mass., President of the American College of Physicians, addressed the February meeting of the Medical Department Officers residing in Washington, D. C., and vicinity at the Sternberg Auditorium of the Army Medical Center, February 16, 1942, on "The Significance and Course of Borderline Abnormalities of Blood Pressure."

Dr. Albert T. Leatherbarrow (Associate), Hampton Station, N. B., who was commissioned a Major in the Medical Corps of the Royal Canadian Army, has been appointed Internist at The Lancaster Military Hospital, Saint John, N. B.

Dr. Herbert J. Rinkel, F.A.C.P., Kansas City, Mo., was the guest lecturer at the University of Texas School of Medicine, at Galveston, February 23–25, 1942. Dr.

Rinkel spoke on "The Nature and Mechanism of Food Allergy," "Methods of Testing Foods," and "The Clinical Application of Food Principles and Food Tests," and also presented a number of kodachromes illustrating the "Etiology of Hay Fever in the Mid-West and Southwest."

Dr. Ramón M. Suárez, F.A.C.P., San Juan, College Governor for Puerto Rico, will be honored by the Medical College of Virginia at its next commencement. Dr. Suárez will receive an honorary degree of Doctor of Science from the College in recognition of his valuable services to medical science in Puerto Rico.

Dr. Manuel de la Pila Iglesias, F.A.C.P., Ponce, has been elected President of the Puerto Rico Medical Association.

Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, has been appointed Acting Director of the Emergency Medical Services in the Civilian Defense of Puerto Rico.

Dr. Richard A. Kern, F.A.C.P., Philadelphia, Pa., was the guest speaker at a recent scientific meeting of the Puerto Rico Medical Association and was unanimously elected an honorary member of the Association.

On January 14, 1942, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "The Relationship of Nutrition to Dentistry" at the annual meeting of the Delaware State Dental Society. On March 4, 1942, Dr. Kelly presented a paper on "The Modern Science of Nutrition and Nutritional Deficiency," illustrated with motion pictures in natural color, at a meeting of the Lancaster County Medical Society in Lancaster, Pa.

On February 17, 1942, Dr. Bernard I. Comroe, F.A.C.P., Philadelphia, Pa., spoke on "Practical Pointers in the Management of the Arthritic Patient" at a meeting of the McKean (Pa.) County Medical Society, and on March 19, 1942, he spoke on "The Use of Physical Therapy in Arthritis" at a meeting of the Pennsylvania Academy of Physical Medicine.

Dr. Harry A. Pattison, F.A.C.P., Livingston, N. Y., has been awarded a prize for submitting an essay on "Peace After War" in a district contest sponsored by the Rotary Club. Dr. Pattison will award the prize he received to the two students at Hudson High School who write the best essays on the same subject.

On March 19, 1942, memorial services were held at the Harvard Medical School for Dr. Soma Weiss, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard University, and Physician-in-Chief, Peter Bent Brigham Hospital, Boston, who died January 31, 1942. Dr. Walter B. Cannon presided and Drs.

Eugene F. Du Bois, F.A.C.P., George R. Minot, F.A.C.P., Eugene B. Ferris, Elliott C. Cutler and William E. Watts spoke at the services.

Dr. George Baehr, F.A.C.P., New York, N. Y., is now Chief Medical Officer in the Office of Civilian Defense, Washington, D. C.

Under the Presidency of Dr. Archibald A. Barron, F.A.C.P., Charlotte, N. C., the North Carolina Neurologic and Psychiatric Association held its regular meeting March 27, 1942, in Charlotte. During the scientific session Dr. Barron conducted a Clinico-Pathological Conference and Dr. Frederick Taylor, F.A.C.P., High Point, N. C., participated in the discussion of a series of case reports.

The National Tuberculosis Association is conducting during the month of April this year's "Early Diagnosis Campaign." The purpose is to focus people's attention on tuberculosis—to find it, treat it, conquer it. More than eight million pieces of printed matter have been prepared and supplied to affiliated associations. Some of these publications relate tuberculosis to the Victory effort, for tuberculosis in a community is like so much sand in the production machinery. The Association will welcome requests for material from all doctors.

Dr. Frank F. D. Reckord, F.A.C.P., Harrisburg, Pa., has been recently appointed the Medical Director of the Harrisburg Hospital.

Dr. George Herrmann, F.A.C.P., Galveston, Texas, delivered the following addresses during April:

"Exigencies of Cardiological Practice" and "Functional Heart Disorders Including the Soldier's Heart" before the Oklahoma State Medical Association on April 22 and 23, respectively.

"Some Medical Emergencies and Their Management" and "Military Aspects of the Cardiovascular System" before the Missouri State Medical Association, April 27 and 28, respectively.

The First National Congress of Internal Medicine of Mexico will be held May 3–10, 1942, under the Presidency of Dr. Teofil Ortiz y Ramirez. Dr. Francisco de P. Miranda, F.A.C.P., and Dr. Ignacio Chavez, F.A.C.P., both of Mexico City, are Vice Presidents. Dr. George Herrmann, F.A.C.P., Professor of Medicine at the University of Texas School of Medicine, Galveston, will present a paper on research work done in the cardiovascular department of the University of Texas.

The Eighteenth Scientific Meeting of the American Heart Association will be held June 5 and 6, 1942, at Chalfonte-Haddon Hall, Atlantic City, N. J.

An intensive course in Tropical Medicine will be given at the New York Post-Graduate Medical School, New York City, for a period of five days, May 25–29, 1942, under the direction of Dr. Z. Bercovitz, F.A.C.P. The course will be a survey of the fundamentals of the various subjects in tropical medicine, and a presentation of the more recent advances that have come from research. Authorities in their respective fields will give lectures and demonstrations in their specialties. Emphasis will be placed on clinical features. Clinical and laboratory material is available for study and demonstration, and an opportunity will be given students for practical work in clinical parasitology.

OBITUARIES

DR. SOMA WEISS, F.A.C.P., 1928

(This obituary is republished from the *Harvard University Gazette* of March 7, 1942 with their kind permission.)

The first shock of the news of the sudden death of Soma Weiss on January 31, 1942, caused among his friends and colleagues the almost universal reaction expressed in words by one, "It is incredible, he was so much alive." Indeed, his vital personality, boundless energy, and excellent health did make him seem to be invulnerable; and his sincere, spontaneous and personal interest in all those with whom he came in contact made his death also the death of something in their lives.

He was born in Bestercze, Hungary, on January 27, 1899. During the dark years of the War and of the disintegration of the Austro-Hungarian Empire he attended the Royal Hungarian University at Budapest, where he was appointed Demonstrator and Research Fellow in Physiology and later in Biochemistry. In 1920 he came to New York. He received the degree of Bachelor of Arts from Columbia in 1921 and only two years later was graduated from Cornell University Medical School as one of its finest products. There he came to know Dr. Eugene F. DuBois as teacher and as a friend through the years. While a student he also held an appointment as Assistant in the Department of Pharmacology of Cornell University. Working at first under the guidance of Dr. Robert Hatcher, he soon published fundamental observations on the reflex nature of the emetic action of digitalis. The interest in the action of drugs so acquired was to continue as an outstanding characteristic of his entire subsequent clinical career.

After graduation he spent two years as intern at the Bellevue Hospital. There he not only received a wide and immediate experience in bedside medicine, but also acquired an understanding of the meaning of that active quality of sympathy for suffering which is expressed by the physician by devoted and intelligent care of the sick. In 1925 he joined the group of young physicians attracted by Dr. Francis W. Peabody to the newly opened Thorndike Memorial Laboratory of the Boston City Hospital. From his first days there to the end of his fourteen years at that hospital, he devoted himself whole-heartedly to the success of the Thorndike and its associated teaching services. His first appointment in the Department of Medicine was as Research Fellow. He rose in only seven years to the rank of Associate Professor—a title perfectly descriptive of his devoted relationship to Dr. Peabody's successor, Professor George R. Minot. In 1932, on Dr. Minot's recommendation, Dr. Weiss was appointed Director of the Second and Fourth Medical Services. In this position his tact and persistence enabled him to make progressive improvements in the clinical services amidst the complexities inherent in the administration of a large municipal hospital. In order to draw together in a common interest in medicine and in the City

Hospital the many interns of the Boston University, Harvard, and Tufts Medical Services, he for several years conducted a fortnightly Grand Round, on which were presented and discussed patients of interest from those various services. Thus, his thinking extended beyond the welfare of the Harvard Unit alone and included a vision of the greatness of the City Hospital as well.

Soma Weiss' contacts with his interns and students were especially close. His ward rounds, conferences and lectures were always popular; and his interest in therapeutics was especially welcome to students. His excellent powers of observation, wide clinical and research experience, and knowledge of the American and foreign literatures, allowed him to contribute significantly to any discussion in the laboratory or at the bedside. He was always in demand as a consultant on various of the hospital services and would answer such calls, when necessary, in the small hours of the night with the freshest interest in the problem presented by the patient.

In 1939 Soma Weiss left the City Hospital to succeed Dr. Henry A. Christian as the second Physician-in-Chief to the Peter Bent Brigham Hospital and the eighth of the distinguished line of those who have held the title of Hersey Professor of the Theory and Practice of Physic in the Harvard Medical School. For the post of the Professor of Medicine in the hospital so closely associated with the Medical School he was, because of his many and varied interests, a particularly fitting choice as one who should continue and foster the development of mutually stimulating relationships between these institutions.

Soma Weiss' chief research contributions were in pathological physiology of cardiovascular disease and in clinical pharmacology and therapeutics. They are contained in nearly two hundred publications replete with data especially from painstaking studies on the patients. Dominant in his work was the concept of a mechanism to be proved or disproved. The selection of problems, often suggested by shrewd observation on the wards, seemed to present no difficulty to his active imagination, and his ability to avoid the blind avenues which appear to open so temptingly in the course of experiment, was uncanny. His collaborators included men representative of several branches of medicine, using the word in the broad sense in which he conceived it: pathology, roentgenology, physiology, neurology, surgery, biochemistry and obstetrics. His predominant and constant activity in making original observations rendered him loath to take the time to write summary articles or books. He did, however, contribute a few chapters to systems of medicine, and shortly before his death published, with Dr. Lewis Dexter, a comprehensive monograph on the toxemias of pregnancy. He took the keenest of interest in the intellectual development of the youg men who came to work with him. Today many of them hold important posts in academic medicine in this country and abroad.

Men like Soma Weiss do not exert an influence on their fellows by their

ideas alone. Thus, his self-reliance, kindness, enthusiasm for living, and sense of humor were felt by all who knew him. These qualities may have been the result of his having lived on two continents, seen much of sickness and misfortune, and found many friends. He took a deep satisfaction in the life of his family, who enriched the sense of welcome felt by the many friends and strangers invited to his home. His death at forty-three terminated a career short in years but long in terms of accomplishment. Soma Weiss' contributions to medicine are spread upon the permanent record of the literature of medical science, but his true memorial is in our hearts.

W. B. C.
R. F.
E. A. S., Jr.

DR. ROCK SLEYSTER

Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., was born at Waupun, Wis., June 14, 1879. He attended local public schools and thereafter entered the University of Illinois College of Medicine, graduating in 1902. He entered the practice of medicine at Kiel and Appleton, Wis., and then became physician to the Prison for the Criminal Insane at Waupun, where he did research, much of it reported later in medical periodicals. In 1903 he became Secretary of the Calumet County Medical Society, continuing for six years, and from that time forward was continuously associated with organized medicine and numerous medical societies. In 1910 he became Assistant Secretary of the State Medical Society of Wisconsin, serving four years, then becoming Secretary. In this post he continued until elected President in 1924. The next year he became Treasurer, serving for many years. Dr. Sleyster was Editor of the Wisconsin Medical Journal from 1918 to 1923; Delegate to the American Medical Association, 1913–1914 and 1918–1926; Vice Speaker of the House of Delegates of the American Medical Association, 1922–1926; Trustee, 1926–1937; Acting Chairman of the Board, 1935–1937; President, 1939–1940.

Dr. Sleyster was Medical Director of the Central State Hospital for Insane, Waupun, 1909–1919; Medical Director, Milwaukee Sanitarium, 1919 to the time of his death; during World War I, Major, Medical Corps, U. S. Army; Medical Aide to the Governor of Wisconsin; Chief of the Bureau of Postgraduate Medical Instruction, University of Wisconsin Extension Division, 1916–1920; member, American Psychiatric Association, Association for Research in Nervous and Mental Diseases and the Central Neuropsychiatric Association. He had been a Fellow of the American College of Physicians since 1924, serving as the College Governor for Wisconsin from 1926 to 1940. He died March 7, 1942, at his home in Wauwatosa, Wis., of heart disease, aged 62.

Personal relations of friendly intimacy conceivably do influence fair judgment, and may create a bias in favor of one's thesis. I confess to a

bias when endeavoring to put into words any characterization of a man so gifted, a friend so loyal, a personality so rarely lovable, as was Rock Sleyster.

It was during my incumbency in the editorial management of *The Wisconsin Medical Journal* that attention was first focused upon the secretary of a small upstate county medical society. He leaped into prominence by editing a column that early demonstrated traits that brought him to the forefront in later years: a ripe, understanding nature, a sincere devotion to and student of his fellowman, a mind of rare judicial maturity—instinctive rather than acquired—all rare qualities in one so young, but qualities that constituted the keystone of his later success in institutional management. He was ideally cast in the latter rôle, for here was his opportunity to capitalize these qualities, coupled with organizational capacity that followed his career to its zenith.

The Presidency of the American Medical Association was greatness thrust upon Dr. Sleyster, an honor not of his seeking. The office sought a man who could control the confidence of the entire profession—this at a time when matters of far-reaching importance were at stake. And the choice was an uncontested one—a rare expression of professional unanimity for a post of national importance.

Rock's organizational ability, as shown in national affairs, was equally exhibited in the home institution which he created and guided so successfully, and nothing could be a more eloquent tribute than the loyalty with which his staff of associates reciprocated their leader's inspiration. He lived to witness the fruition of the ideal to which he had dedicated the years of his productivity; and though in later years physically incapacitated from as full participation in affairs as he may have wished, he guided in his quiet unobtrusive way, with a steady hand, and a mind alert to the end. Fittingly expressed is Emerson's "An institution is the lengthened shadow of one man."

I might stress another angle of Rock's character that reflects the unique position he had won in this community: his advice was being constantly sought by medical friends from far and near, and he lent a ready ear to such requests—flattered but pleased because these advances evinced a confidence in his integrity of thought and sincerity of action that are the allotted boast of few men. What memorial is more to be cherished than the knowledge that one has gained the respect, the esteem, and the love of his fellowmen?

Rock Sleyster's death was a shock to those who enjoyed his intimate contact and friendship; his lovable character is a happy memory; his influence on his surroundings remains as an enduring monument to his greatness.

ARTHUR J. PATEK, M.D., F.A.C.P.

DR. MARTHA TRACY

One of the most distinguished members of the medical profession, Dr. Martha Tracy, passed away on Sunday, March 22, at the Woman's Medical College Hospital.

Dr. Tracy, born in Plainfield, N. J., in 1876, attended Plainfield Seminary, Bryn Mawr College, the University of Pennsylvania and Woman's Medical College of Pennsylvania. She attained, through her contributions to the profession and her unfailing interest in organized medicine, a position of honor and esteem not only in Philadelphia but throughout the entire nation. This outstanding woman never, throughout her entire career, failed to answer the urgent call of her chosen field whether as scholar, teacher or public health official.

Dr. Tracy served as Associate Professor of Chemistry at the Woman's Medical College from 1909 to 1913, at which time she assumed Professorship of Physiological Chemistry until 1921. From 1921 until 1923 she served as Professor of Hygiene and then became Professor of Preventive Medicine until 1931. This great medical school advanced under her dignified and learned leadership during the time she served as Dean from 1918 to 1940.

In 1940 Philadelphia was most fortunate in having Dr. Tracy accept the position as Assistant Director of Public Health. Prior to her position as Assistant Director of Health, Dr. Tracy served for many years as Director of the Philadelphia Health Council and Tuberculosis Committee.

Since 1923 Dr. Tracy has been a Fellow of The American College of Physicians, always keenly interested in its activities. She likewise served the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, the Medical Women's National Association and the College of Physicians in Philadelphia.

It is with much sorrow and regret that we acknowledge the passing of this most beloved friend of medicine.

EDWARD L. BORTZ, M.D.,
Governor for Eastern Pennsylvania.

DR. LEROY S. PETERS

One of the most highly respected and best loved physicians of our State passed away December 17, 1941, as a result of a coronary occlusion.

Dr. Peters was born April 6, 1882, at St. Joseph, Michigan. He graduated from the public schools at St. Joseph and took his academic work at the University of Minnesota. He received his medical degree at the University of Illinois College of Medicine in 1906.

Dr. Peters came to New Mexico in 1909. He came, as did many of the medical profession, with pulmonary tuberculosis, hoping to be benefited by the climate. He regained his health at Silver City, and when he was able to work he began as Assistant Medical Director of the Cottage Sanatorium in that city. In 1913 he came to Albuquerque and was associated with the late Dr. A. G. Shortle as Director of the Albuquerque Sanatorium; he was later Director of St. Joseph's Sanatorium. He was on the active staff of St. Joseph's and the Presbyterian Hospitals from the time the staffs were first organized. He was a Director of the National Tuberculosis Association

for many years; he was past President of the American Sanatorium Association and the Southwestern Medical Association. He had served as President of his County and State Societies. He was a Licentiate of the American Board of Internal Medicine, and a Fellow of the American College of Physicians since 1927, serving as Governor for New Mexico since 1931.

Dr. Peters was the author of many published papers and was one of the outstanding authorities on pulmonary conditions in the country. He was an indefatigable worker, and it was due to the efforts of men like him that we saw the great fall of the death rate of tuberculosis during his period of activity. He attended all medical meetings of the organizations to which he belonged, and was guest speaker at many others.

His wife and one son survive him.

MELDRUM K. WYLDER, M.D., F.A.C.P.

DR. FRANK LEECH

Dr. Frank Leech, F.A.C.P., long a prominent pediatrician, Life Member and former President of the Medical Society of the District of Columbia, died February 4, 1942, at Walter Reed General Hospital, following a long illness. Funeral services were held on February 10 with the Rev. Dr. Frederick Brown Harris of Foundry Methodist Church, and Dr. Leech's brother, the Rev. H. Bishop Leech of Paterson, New Jersey, officiating.

Dr. Leech was born in Prince Georges County, Maryland, on January 14, 1870, the son of the Rev. Dr. George Vanderlip Leech. He attended St. John's College at Annapolis and Ohio Wesleyan University. He received his medical degree from Columbian University, now George Washington, in 1891, and served his internship at Garfield Memorial Hospital where he later became a member of the consulting staff. At Children's Hospital he served in various capacities from 1892 until his retirement in 1938. At that time Dr. Leech was honored by a tablet citing his distinguished services to the institution, and his friends established in his honor the Frank Leech Laboratory Fund.

At the outbreak of the first World War, Dr. Leech volunteered and was commissioned a Major in the Medical Corps. He was placed in charge of the medical departments at Camp Sevier and Fort Sill, Oklahoma. He was later commissioned a Lieutenant Colonel in the Medical Reserve Corps. He held memberships in the Reserve Officers Association, the Military Order of the World War, and the American Legion.

Dr. Leech was Past President not only of the Medical Society of the District of Columbia, but of the Clinico-Pathological Society of Washington. He was a member of the American Medical Association, the Southern Medical Association and the George Washington Medical Society. He had been a Fellow of the American College of Physicians since 1923. He was one of the founders of the American Academy of Pediatrics.

In the death of Dr. Frank Leech the Medical Society of the District of

Columbia has lost a member who was replete with medical knowledge and seeped with the wisdom of experience.

Dr. Leech had an exceptional capacity for sustained friendship—a friendship constant, without variation or shadow of turning. To experience the richness of his companionship was a joy.

He met the issues of life unafraid, resolving its complexities into simple formulae. He wove the multicolored tapestry of life into the concrete realities of every day.

His enduring qualities were love and service. Never loosening his hold of the magnetic chain of humanity, he made barren places fruitful with kindness.

EDWARD Y. DAVIDSON, M.D.

DR. ISADORE JULIUS WOLF

Dr. Isidore Julius Wolf, of Kansas City, Missouri, died December 17, 1941, of cerebral hemorrhage. Dr. Wolf was born in Stuttgart, Germany, and was graduated from the University of Munich and Heidelberg, 1887. He came to Kansas City in 1888, took postgraduate work at the Chicago Post Graduate School in 1889, and later did postgraduate work at the New York Post-Graduate Medical School and at the University of Vienna. From 1895 to 1905 he was successively Instructor in Bacteriology, Instructor in Medicine and Professor of Medicine at the University Medical College, Kansas City, Missouri. In 1905 he became Professor of Medicine at the University of Kansas School of Medicine. He retired about two years before his death and upon his retirement was made a Professor Emeritus. For many years he was Head of the Medical Department of the Alfred Benjamin Dispensary, and a member of the St. Joseph Hospital staff; he was a member of the Menorah Hospital staff, serving as President of that staff in 1938, and consulting Physician to the Kansas City General Hospital. He was a member of the Jackson County Medical Society and Missouri State Medical Society, and had been an Associate of the American College of Physicians almost since its inception. Dr. Wolf enjoyed a large practice for many years and wrote two books, "The Human Fuel" and "A Family Doctor's Note Book." He retired from active practice several years ago on account of failing health.

Dr. Wolf is survived by his wife, Mrs. Leah Marks Wolf, and three sons, Robert E. Wolf, Dr. Jack W. Wolf and I. James Wolf.

A. C. GRIFFITH, M.D., F.A.C.P.,
Governor for Missouri.